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# Une approche multi-échelle des processus écologiques et évolutifs impliqués dans le cancer

Tazzio Tissot

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# THÈSE POUR OBTENIR LE GRADE DE DOCTEUR DE L'UNIVERSITÉ DE MONTPELLIER

En Sciences de l'Évolution de la Biodiversité

École doctorale GAIA

Unité de recherche Maladies Infectieuses et Vecteurs :  
Écologie, Génétique, Évolution et Contrôle

## Une approche multi-échelle des processus écologiques et évolutifs impliqués dans le cancer

Présentée par Tazio TISSOT  
Le 16 octobre 2017

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UNIVERSITÉ  
DE MONTPELLIER





Don't give in without a fight.

---

Roger Waters,  
*The Wall*



## Avant-propos

La vie est un mouvement perpétuel, souvent pour rester à la même place. Aussi, j'ai toujours pensé que je ferai ma carrière dans le milieu académique, parce que je ne veux rien d'autre que connaître et comprendre. J'aurais pu suivre ces voies : parce qu'à travers la science, je vis un million de vies, dans un million de lieux, dans un million d'époques. L'enchaînement des événements passés, leurs causes, et les règles générales de fonctionnement du monde ; tout ce que j'ai toujours voulu. J'ai longtemps pensé que je deviendrais historien ou physicien. Finalement, je me suis perdu dans les sciences de l'écologie et de l'évolution. Plus j'ai exploré ce labyrinthe, plus il s'est agrandi. Je ne pourrai jamais en sortir. Et merde, qu'est-ce que j'aime ça !

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## Partie I

# Introduction

## 1 Introduction à la biologie du cancer

### 1.1 Le cancer est une pathologie

**Un bref historique de l'oncologie** La lignée humaine a été confrontée extrêmement tôt au cancer, puisque cette pathologie se retrouve au cours de la préhistoire, dès les premiers Hominiens il y a 1.7 millions d'années (Odes et al. 2016). Néanmoins, les premières traces écrites faisant mention de cancer se retrouvent au Proche-Orient durant la Haute Antiquité : notamment, les papyrus Edwin Smith (-3000) et Ebers (-1500) contiennent les premières descriptions de tumeurs du sein, de la peau, du pharynx, de l'estomac, du rectum et de l'utérus, mais concluent à l'époque que la maladie est incurable (Hajdu 2004). Au IV<sup>e</sup> siècle avant notre ère, Hippocrate sera le premier à nommer la pathologie sous le nom que nous lui connaissons, comparant ainsi les extensions de la tumeur aux longs appendices du crabe (*karkinos/karkinoma*). Hippocrate préconise ainsi la résection chirurgicale ou la cautérisation, pour venir à bout de la maladie (Hajdu 2004). Au Moyen-Âge, la résection chirurgicale sera également le principal traitement administré aux patients cancéreux sur le pourtour méditerranéen. Néanmoins, l'efficacité thérapeutique sera particulièrement améliorée par la description de plus en plus précise des tumeurs, et lorsque fut découverte la nécessité d'extirper l'entièreté de la tumeur afin que le patient soit guéri (Hajdu 2011).

A l'époque moderne, la découverte et la description du système lymphatique permirent à de nombreux médecins européens d'identifier et prévenir les lésions entraînant la mort des patients. C'est également à cette époque que médecins et biologistes commencent à identifier les origines du cancer, créant ainsi les bases de l'épidémiologie du cancer : au XVIII<sup>e</sup> siècle, Percival Pott décrit ainsi le cancer du scrotum des ramoneurs et John Hunter identifie les premiers cancers héréditaires. Virchow est le premier, en 1858, à identifier l'origine du cancer parmi les cellules de l'organisme (Virchow 1859).

A partir du début du XX<sup>e</sup> siècle, les avancées thérapeutiques sont de plus en plus importantes. Les travaux de Röntgen et des Curie sur le rayonnement permettent le développement de la radiothérapie dès 1904. De même, à partir des années 1940, plusieurs médecins et pharmacologues explorent indépendamment le ré-emploi en oncologie d'armes chimiques, dont l'effet cytotoxique diminue la croissance tumorale. Dès lors, chirurgie, radiothérapie et chimiothérapie forment le corpus classique de thérapies utilisées en oncologie. Ce corpus sera amélioré par la suite, et complété par des traitements de plus en plus précis (immunothérapie, hormonothérapie, etc).

**Les manifestations cliniques du cancer** Le cancer se manifeste généralement par la prolifération cellulaire incontrôlée. Cette prolifération peut se manifester par la formation d'une tumeur, c'est à dire par l'augmentation de volume d'un tissu. Le cancer peut donc être détecté par l'augmentation de volume d'un organe. Mais il peut également être détecté, en biopsie, par des marqueurs cellulaires de prolifération. Contrairement aux hyperplasies (tumeurs bénignes) dont la croissance est limitée, les néoplasies (tumeurs malignes cancéreuses) ont une croissance rapide et envahissent rapidement les tissus avoisinants. Une néoplasie peut également essaimer dans le reste de l'organisme : des cellules cancéreuses peuvent essaimer par les systèmes sanguins et lymphatiques jusqu'à d'autres organes, où elles forment des tumeurs secondaires (métastases). Ainsi, du fait de l'invasion des tissus, le cancer peut également être détecté par les perturbations physiologiques chez le patient, parmi lesquelles :

- la tumeur peut comprimer les terminaisons sensorielles et être à l'origine de douleurs
- elle peut comprimer un organe tubulaire et perturber la digestion, la respiration, etc.
- elle peut blesser les tissus, et provoquer des saignements répétés

Ces manifestations, si confirmées en anatomopathologie, sont le signe d'un cancer invasif, ayant déjà progressé à un stade avancé. Néanmoins, plusieurs méthodes permettent de rechercher préventivement les manifestations de cancer à des stades subcliniques. Les tissus les plus externes peuvent être palpés pour recherche de tumeurs, et parallèlement l'imagerie médicale<sup>1</sup> aide à détecter des corps denses au sein des tissus internes.

Chez un patient, les manifestations potentielles de la maladie peuvent être graves et généralisées au fur et à mesure que le cancer progresse de stade en stade. La croissance de la tumeur et le processus invasif causent de nombreux troubles organiques et fonctionnels dans les organes touchés. La modification de la balance hormonale modifie en profondeur la physiologie du patient : il peut être atteint d'immunosuppression (Almand et al. 2001; Wolf et al. 2003), et subir une perte de poids rapide et généralisée (Tisdale 2002). Les troubles psychologiques et du sommeil sont également fréquents (Chochinov 2001; Lowery 2015).

La létalité du patient cancéreux dépend de l'organe touché, du stade auquel le cancer est pris en charge, et de la condition physique du patient. Ainsi, le taux de survie à 5 ans est de 87% pour les patients atteints d'une tumeur mammaire, mais de seulement 19% pour les patients atteints d'une tumeur cérébrale. Pour ces derniers, 60% d'entre eux survivent au moins 5 ans s'ils ont moins de 40 ans au diagnostic, mais 1% seulement au delà de 80 ans<sup>2</sup>.

**Traitement clinique du cancer** La guérison du cancer revient à réduire le risque de re-développer une tumeur jusqu'à atteindre celui de la population générale non cancéreuse, ce qui passe généralement par une élimination complète de la (ou les) tumeur(s). Pour ce faire, il est souvent indispensable d'effectuer une résection chirurgicale des tissus cancéreux. Néanmoins, l'ablation se doit d'être la plus localisée possible, de sorte à ne pas enlever des tissus sains indispensables à la survie ou la bonne santé du patient (tumeur cérébrale ou osseuse par exemple) : une réduction préalable de la taille de la tumeur peut être nécessaire. De même, la tumeur peut être trop étendue ou placée dans un organe trop complexe à opérer, pour que tous les tissus puissent être éliminés chirurgicalement. Il est donc souvent nécessaire de procéder à des traitements complémentaires, antérieurement et/ou postérieurement à la chirurgie.

Pour ce faire, la radiothérapie et la chimiothérapie sont les traitements les plus couramment utilisés (aux côtés des thérapies, des immunothérapies, etc.). La radiothérapie consiste à exposer localement les tissus cancéreux du patient à des rayonnements ionisants (rayons X ou gamma), bloquant ainsi leur capacité de réplication. Elle permet un traitement ciblé de la tumeur, mais présente des risques de radiotoxicité. La chimiothérapie anticancéreuse consiste à exposer toutes les cellules à prolifération rapide, au premier rang desquelles les cellules cancéreuses, à des substances cytotoxiques (agents alkylants, antimétabolites, hormones, etc.). Néanmoins, ces substances peu spécifiques affectent souvent les cellules saines, et peuvent donc être mal supportées par les patients.

Quelle que soit la combinaison de traitements employés, il est fréquent qu'ils ne réussissent pas à éliminer l'intégralité des tissus malades. Un petit nombre de cellules cancéreuses résistant au traitement suffit alors à reconstituer une tumeur entière, et à provoquer la récurrence du cancer.

<sup>1</sup>Radiographie, échographie, tomographie, scintigraphie, imagerie par résonance magnétique nucléaire, tomographie par émission de positons, etc.

<sup>2</sup>Statistiques 2010-11 pour l'Angleterre et le Pays de Galles, <http://www.cancerresearchuk.org/health-professional/cancer-statistics/>

## 1.2 Le processus cancéreux

**Un processus dynamique : de l'initiation à la métastase** Le cancer est le plus souvent une pathologie de temporalité lente : elle suit une progression sur plusieurs étapes obligatoirement successives, dont le passage de l'une à l'autre repose sur un processus aléatoire. De l'initiation de cette prolifération au moment du diagnostic se passe une durée de l'ordre de la dizaine d'années (Beerenwinkel et al. 2007).

Les premières étapes de **cancérogenèse** réalisent la transformation de cellules saines en cellules cancéreuses. Ainsi, durant l'initiation, les cellules perdent leur capacité à effectuer l'apoptose, deviennent insensibles aux signaux pro-apoptotiques, et dérèglent leur cycle cellulaire (Gatenby and R. J. Gillies 2008). La promotion pérennise ensuite les transformations acquises durant l'initiation, notamment par une dérégulation profonde du génome.

La formation de la tumeur (**tumorigenèse**) réclame la permissivité du stroma : c'est à dire la stimulation de la progression cancéreuse par les cellules saines. Ainsi, un cancer *in situ* pratique l'angiogenèse (formation de vaisseaux sanguins *de novo*) et la production de facteurs de croissance. Le cancer devient **invasif** dès lors que la croissance tumorale s'étend au delà des lames basales. L'invasion des tissus environnant se poursuit jusqu'aux circulations sanguine et lymphatique, à partir desquelles le cancer peut proliférer dans d'autres organes (sous forme de **métastase**).

**Le phénotype de la cellule cancéreuse** Bien que la majorité des cancers soient d'origine ectodermique, cette pathologie peut en fait provenir de tout tissu de l'organisme, et les pathologies diffèrent énormément selon la cellule d'origine. Néanmoins, les cellules cancéreuses partagent des caractéristiques phénotypiques communes, largement connues sous le nom de *hallmarks of cancer* (Hanahan and Weinberg 2000, 2011).

Ces caractéristiques, acquises au cours de la progression cancéreuse, sont au nombre de six : l'autosuffisance en signaux de croissance, l'insensibilité aux signaux inhibiteurs de la croissance, la capacité à éviter l'apoptose, la capacité de se répliquer indéfiniment, l'induction de l'angiogenèse, et la capacité à former des métastases (Hanahan and Weinberg 2000). On y ajoute régulièrement deux caractéristiques phénotypiques supplémentaires : la dérégulation du métabolisme énergétique cellulaire et la capacité à éviter une destruction par le système immunitaire. L'ensemble de ces caractéristiques apparaissent sous l'influence de l'inflammation et de l'instabilité génomique (Hanahan and Weinberg 2011).

**Le génotype des cellules cancéreuses** La transformation de cellules saines en cellules cancéreuses est avant tout basée sur le processus de mutation somatique. Les mutations impliquées dans la progression cancéreuse (mutations *drivers*) touchent généralement trois familles de gènes :

- Les proto-oncogènes (p. ex. *myc*, *ras*, *abl*) sont des régulateurs positifs de la prolifération cellulaire. Le gain de fonction de ces gènes stimule la division cellulaire ou inhibe l'apoptose.
- Les gènes *gatekeepers* (p. ex. *p53*, *Rb*) sont des régulateurs du cycle cellulaire. La perte de fonction de ces gènes favorise la croissance cellulaire incontrôlée.
- Les gènes *caretakers* (p. ex. *brca1/2*, *atm*) participent à l'intégrité du génome. Leur perte de fonction n'influence pas directement la prolifération cellulaire, mais favorise l'accumulation de nouvelles mutations. Cette dernière catégorie de gènes est, avec les *gatekeepers*, regroupée sous le terme générique de *gènes supprimeurs de tumeurs*.

Ces mutations, lorsqu'elles sont accumulées selon une séquence spécifique, favorisent la prolifération des cellules cancéreuses (Fearon and Vogelstein 1990).

Ainsi, le cancer est caractérisé par une très forte instabilité génomique. Le génome cancéreux peut notamment différer du génome sain par plus de 1000 mutations ou épimutations (Vogelstein, Papadopoulos, et al. 2013). On peut également retrouver de nombreux exemples de polyploïdie, d'aneuploïdie et d'aberrations chromosomiques parmi les cellules cancéreuses (Davoli et al. 2017; Dewhurst et al. 2014). Du reste, l'accumulation des modifications génomiques est indépendante d'une cellule à l'autre, ce qui résulte en une très forte hétérogénéité génétique au sein de chaque tumeur, ainsi que d'une tumeur à l'autre (Marusyk and Polyak 2010; Vogelstein, Papadopoulos, et al. 2013).

### 1.3 Causes intrinsèques et extrinsèques du cancer

Le processus cancéreux est nourri par les mutations dérégulant le cycle cellulaire, et par un contexte tissulaire favorable à la prolifération cellulaire. En cela, tout facteur influençant ces deux paramètres est susceptible de moduler le risque de développer un cancer.

#### 1.3.1 Causes intrinsèques

**Les risques héréditaires** Si tout individu peut développer un cancer, on retrouve davantage d'individus touchés dans certaines familles, et généralement pour un type de cancer donné. Il existe donc des risques héréditaires à développer certains cancers. Si la grande majorité des mutations impliquées dans la cancérogenèse sont acquises, certaines peuvent toucher la lignée germinale et se transmettre d'une génération à l'autre. Ainsi, dès leur naissance, certains individus possèdent déjà au moins une des mutations impliquées dans la progression cancéreuse, et le temps d'accumuler les autres s'en retrouve réduit.

Ces mutations pro-oncogéniques héréditaires touchent les trois familles de gènes citées plus haut (section 1.2). Ainsi, un allèle du proto-oncogène *Ret* augmente le risque de néoplasie endocrinienne multiple de type 2 (S. C. Huang et al. 2000), un allèle du *gatekeeper Rb* celui de rétinoblastome (Bandara and La Thangue 1991), et un allèle du *caretaker BRCA1* celui de cancer du sein (King, Marks, and Mandell 2003).

**Les risques anatomiques** L'incidence du cancer varie d'un organe à l'autre. Ainsi, certains sont très rarement touchés : pour 100,000 habitants, on compte 2 cas pour les testicules, 2.2 cas pour l'intestin grêle, et 6 cas pour le cerveau. D'autres le sont beaucoup plus souvent : pour 100,000 habitants, on comptera 23.8 cas pour la peau, 57.3 cas pour les poumons, et 67.2 cas pour les seins<sup>3</sup>.

De surcroît aux susceptibilités génétiques individuelles, plusieurs facteurs peuvent expliquer ces tendances. D'une part, l'expression du génome diffère d'un organe à l'autre. Si un organe exprime davantage certains gènes potentiellement touchés par des mutations pro-oncogéniques, cet organe sera statistiquement davantage touché par le cancer (Muir and Nunney 2015). D'autre part, tous les organes ne renouvellent pas leurs cellules à la même vitesse : dans l'espèce humaine, la durée de vie d'un kératinocyte est de 40 à 56 jours (Halprin 1972), tandis que les neurones peuvent vivre plusieurs dizaines d'années (Nowakowski 2006). Par conséquent, le nombre de divisions des cellules souches diffère d'un organe à l'autre, et avec lui la probabilité qu'une erreur de réplication touche un gène impliqué dans le cancer (Tomasetti and Vogelstein 2015).

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<sup>3</sup>Données pour les Etats-Unis entre 2009 et 2013, <http://seer.cancer.gov/>



### 1.3.2 Causes extrinsèques

**Les risques environnementaux** Outre les risques intrinsèques à développer un cancer, de nombreux risques d'origine environnementale existent. On retrouve au premier rang d'entre eux l'exposition à tout agent mutagène, susceptible d'induire des mutations dans des gènes impliqués dans la cancérogenèse. Ainsi, des phénomènes physiques (p. ex. rayonnement ultra-violet B, Césarini 2007) ou des substances chimiques (p. ex. benzène, Ward Jr. et al. 1992) sont susceptibles d'induire des mutations dans le matériel génétique des cellules qui y sont exposées.

D'autres facteurs environnementaux, sans provoquer de mutagenèse somatique, peuvent rendre certains tissus permissifs au développement de tumeurs. Notamment, les hormones produites chez une personne à l'alimentation excédentaire (leptine, insuline, IGF-1, etc.) participent à favoriser la prolifération cellulaire et à inhiber l'apoptose (Vucenik and Stains 2012).

**Les risques infectieux** Des agents mutagènes d'origine biologique sont connus de longue date (p. ex. aflatoxine produite par *Aspergillus*, Wong and Hsieh 1976), mais l'infection elle-même peut augmenter le risque de développer un cancer. En effet, certains cancers sont associés de manière très étroite à l'exposition à des agents infectieux (Paul W Ewald 2009; Martel and Franceschi 2009), parmi lesquels :

- le papillomavirus humain avec le cancer du col utérin
- les virus des hépatites B et C avec le carcinome hépatique
- la bactérie *Helicobacter pylori* avec le cancer de l'estomac
- le virus d'Epstein-Barr avec le lymphome de Burkitt, le lymphome T centro-facial, le carcinome nasopharyngé, et la maladie de Hodgkin

Bien d'autres agents infectieux présentent un risque soupçonné ou avéré de cancer, à tel point que les estimations minimales sur la proportion de cas de cancers provoqués par des agents infectieux sont d'environ 15-20% (jusqu'à 80% pour certains auteurs, Martel, Ferlay, et al. 2008).

Les mécanismes par lesquels les agents infectieux favorisent l'émergence de cancer sont multiples. La mutagenèse peut être favorisée directement par insertion directe de séquences virales dans le matériel génétique, ou indirectement par l'exposition aux sécrétions bactériennes. Les infections peuvent également favoriser la permissivité des tissus à l'installation de tumeurs : la stimulation de l'inflammation par les infections chroniques (Karin, T. Lawrence, and Nizet 2006) ou l'affaiblissement du système immunitaire par les virus de l'immunodéficience humaine (Whitby et al. 1995) créent un terrain propice au développement de tumeurs.

## 2 Ecologie et évolution du processus cancéreux

Oncologues et biologistes ont longtemps étudié le cancer sous l'angle fonctionnel. Les travaux pionniers de John Cairns (Cairns 1975) et Peter Nowell (Nowell 1976) ont démontré l'intérêt d'utiliser les enseignements de la biologie de l'évolution comme approche complémentaire pour comprendre la progression du cancer, de l'initiation à la métastase.

## 2.1 La cellule cancéreuse, une unité de sélection

Le processus cancéreux se produit dès lors que la sélection naturelle favorise l'émergence de variants proliférant davantage que les autres au sein d'une population de cellules (c'est à dire au sein d'un tissu, Greaves and Maley 2012).

**Origines des modifications phénotypiques** L'origine première de la variation phénotypique qui nourrit le processus de sélection dans le cancer est la mutagenèse somatique. Globalement, de nombreux gènes sont mutés durant le processus cancéreux, mais tous ne sont pas impliqués de la même manière dans l'évolution des cellules cancéreuses. Notamment, la génomique du cancer tend à classer les mutations selon leur effet sur la progression cancéreuse : les mutations/gènes *drivers* ont un effet bénéfique sur la prolifération cellulaire, au contraire des mutations/gènes *passengers* qui restent neutres ou délétères pour les cellules (Vogelstein, Papadopoulos, et al. 2013). Il semble que peu de mutations dans le génome cancéreux soient réellement impliquées dans la prolifération cellulaire (p. ex. Tomasetti and Vogelstein 2015), surtout du fait de l'apparition de phénotypes mutateurs (dûs à la perte de fonction des gènes *caretakers*, Negrini, Gorgoulis, and Halazonetis 2010) qui fournissent un grand nombre de mutations *passengers* (McFarland, Mirny, and Korolev 2014). Il faut toutefois garder à l'esprit qu'un allèle neutre ou délétère dans un environnement peut devenir bénéfique dans un autre, et que cette classification n'est pas rigide.

Des changements non génétiques sont également impliqués dans l'apparition de nouveaux phénotypes cellulaires, notamment du fait des modifications micro-environnementales. Ces modifications peuvent être indépendantes du processus cancéreux, comme l'inflammation chronique et l'inflammation sénescence-dépendante qui modifient la prolifération des cellules avoisinantes (Coussens and Werb 2002; Falandry et al. 2014). Elles peuvent également dépendre du processus cancéreux, comme lorsque l'hypoxie induite par croissance tumorale provoque la dé-différenciation cellulaire (Axelson et al. 2005). De manière générale, de nombreux mécanismes de plasticité phénotypique sont impliqués dans l'apparition de nouveaux phénotypes au sein des tumeurs (Magee, Piskounova, and Morrison 2012).

**Les régimes d'évolution au sein des tumeurs** On retrouve au sein des tumeurs des cellules cancéreuses différenciées, mais également des *cellules souches cancéreuses*, dé-différenciées, qui sont responsables de l'essentiel de la croissance tumorale (Weissman 2015). La structuration génétique et phénotypique des tumeurs, et le devenir des différents phénotypes, est donc dépendante : (i) de l'évolution clonale, c'est à dire de l'expansion des phénotypes proliférant le plus dans des conditions écologiques données ; (ii) et de la plasticité phénotypique, c'est à dire de la génération de différents phénotypes à partir d'un seul génotype (Michor and Polyak 2010). En fonction de l'influence relative de chacun des mécanismes, l'évolution de la population à partir d'une cellule initiale pourrait suivre deux dynamiques : soit une évolution linéaire, où la population est toujours relativement homogène et change de manière graduelle ; soit une évolution branchante, où la population se subdivise en plusieurs lignées évoluant de manière indépendante. La grande majorité des tumeurs solides suit une évolution branchante, mais certaines tumeurs liquides peuvent suivre une évolution linéaire (Yates and P. J. Campbell 2012).

Si la plupart des modèles de tumeur suivent une dynamique évolutive branchante, la dynamique d'émergence des différentes lignées semble varier selon les cas. Le régime d'évolution dépend de l'importance relative de la sélection et de la dérive (C.-I. Wu et al. 2016). Dans certains cancers, la diversité émerge très précocement puis stagne (modèles dits de *Big Bang évolutif*, voir Sottoriva, Kang, et al. 2015 pour un exemple de cancer colorectal), et la dérive semble prendre une part importante dans l'évolution de ces cancers (Sottoriva, Barnes, and T. A. Graham 2017; M. J. Williams et al. 2016). Dans d'autres, la diversité émerge continuellement au cours de la progression cancéreuse (voir Gerlinger et

al. 2012 pour le carcinome rénal, Sottoriva, Spiteri, et al. 2013 pour le glioblastome multiforme). La dynamique de ces derniers dépend bien plus de la sélection naturelle, et donc des contraintes micro-environnementales : il est ainsi possible de retrouver les traces de balayages sélectifs (c'est à dire la fixation de mutations avantageuses) au sein du génome cancéreux (Greenman et al. 2007; Maley, Galipeau, Li, et al. 2004). Toutefois, on notera que les cellules cancéreuses ne recombinent pas leurs génomes, et certaines mutations avantageuses peuvent être perdues sur le long terme du fait de l'accumulation des épisodes de sélection (C.-I. Wu et al. 2016).

## 2.2 Les tumeurs sont des écosystèmes

Les tumeurs cancéreuses – qu'elles soient primaires ou secondaires (métastases) – sont constituées d'un ensemble de cellules cancéreuses, vivant et évoluant dans un micro-environnement constitué de matrices, mais également de cellules non cancéreuses (stroma). Envisager cet ensemble comme un écosystème permet de comprendre le devenir des tumeurs, leur évolution et leurs réactions face aux traitements (Merlo et al. 2006).

**Le biotope tumoral : un milieu modelé par et pour les cellules cancéreuses** Le tissu tumoral diffère significativement des tissus non cancéreux, dans sa composition et sa structuration. La simple croissance incontrôlée de populations cellulaires en son sein modifie considérablement les paramètres physico-chimiques et la répartition des différentes cellules. Du fait de l'augmentation de volume, de nombreuses cellules se retrouvent éloignées des vaisseaux sanguins (Cárdenas-Navia et al. 2008; R. J. Gillies and Gatenby 2007) : ces cellules ont donc un accès très limité aux nutriments et au dioxygène, vivant souvent dans des environnements hypoxiques. Cette forte contrainte structure les populations de cellules cancéreuses en fonction de leur capacité à supporter l'hypoxie (Alfarouk, Ibrahim, et al. 2013), et participer ainsi à générer une hétérogénéité spatiale et phénotypique. Néanmoins, les cellules cancéreuses peuvent également développer plusieurs adaptations pour répondre au manque de dioxygène et de nutriments. D'une part, elles peuvent s'assurer d'une meilleure vascularisation de la tumeur, soit en induisant la formation de vaisseaux sanguins *de novo* (angiogenèse, Folkman 2006), soit en formant d'elles-mêmes de nouveaux canaux (mimétisme vasculogénique, Folberg, Hendrix, and Maniotis 2000). D'autre part, elles adoptent souvent un métabolisme glycolytique particulièrement élevé (Gatenby and R. J. Gillies 2004), qui les autorise à vivre dans des milieux pauvres en dioxygène. Ce dernier tend à acidifier le milieu (J. S. Fang, R. D. Gillies, and Gatenby 2008), du fait de la libération massive et continue de lactate. En outre, on notera globalement un fort remodelage du micro-environnement par les cellules cancéreuses pour favoriser leur prolifération, par le biais de la sécrétion de protéases et du dépôt de collagène (Chapman et al. 2014).

**La biocénose tumorale : cellules cancéreuses, cellules saines, cellules recrutées** Au sein de la tumeur co-existent de nombreux variants cancéreux, qui entretiennent un large réseau d'interactions biologiques (Camacho and Pienta 2012). Les ressources étant particulièrement limitées dans la tumeur, les cellules cancéreuses sont régulièrement en compétition les unes avec les autres : pour le glucose et le dioxygène, mais aussi pour les nombreuses hormones et facteurs diffusibles paracrines dont la prolifération dépend. Cette compétition tend donc à favoriser les cellules cancéreuses proliférant le plus rapidement (compétition par exploitation, Nagy 2004), mais aussi les cellules cancéreuses capables d'inhiber la croissance des autres (compétition par interférence, Alfarouk, Muddathir, and Shayoub 2011). Néanmoins, face à la limitation des ressources, on retrouve également de nombreuses interactions mutualistes entre cellules cancéreuses : cette coopération peut impliquer la production de facteurs de croissance

(Marco Archetti, Ferraro, and Gerhard Christofori 2015; R. Axelrod, D. E. Axelrod, and Pienta 2006), tout comme le partage de tâches (Chapman et al. 2014). Néanmoins, dans les cas où ces ressources sont mises en commun dans le micro-environnement, ce mutualisme peut évoluer vers une exploitation par les variants cellulaires qui ne paient pas le coût de la coopération (Marco Archetti, Ferraro, and Gerhard Christofori 2015). Ces interactions peuvent aboutir à la mise en place d’une sélection fréquence-dépendante (Marco Archetti, Ferraro, and Gerhard Christofori 2015; Korolev, Joao B Xavier, and Gore 2014; Marusyk, Tabassum, et al. 2014), autorisant ainsi la co-existence de plusieurs phénotypes.

Au sein de ce réseau d’interactions, il faut également considérer l’ensemble des cellules stromales : fibrocytes, cellules endothéliales, et une grande diversité de cellules immunitaires de lignées myéloïdes et lymphoïdes. Cellules cancéreuses et cellules stromales entretiennent les unes avec les autres un grand nombre d’interactions, qui favorisent ou non la prolifération des cellules cancéreuses (Mueller and Fusenig 2004; Tlsty 2001). Ainsi, si lymphocytes et macrophages tendent à éliminer les cellules cancéreuses (Corthay et al. 2005; Spel et al. 2013), ces dernières les affaiblissent grâce à la compétition pour les ressources (Chang et al. 2015), et les excluent des tumeurs grâce à des interactions amensalistes (Carmona-Fontaine et al. 2013). En revanche, tous les types de cellules stromales peuvent être recrutées par les cellules cancéreuses pour assurer différentes fonctions à moindre coût : production de facteurs de croissance (Tlsty 2001), remodelage de la matrice (Jodele et al. 2006), formation de vaisseaux sanguins (Bergers et al. 2000).

## 2.3 Processus éco-évolutifs et développement de la maladie

Les cellules cancéreuses vivent et évoluent dans un écosystème, qu’elles participent à former (Polyak, Haviv, and I. G. Campbell 2009). Ces processus éco-évolutifs sont à l’origine de la transformation des cellules de l’organisme en cellules cancéreuses, et déterminent la formation et la croissance des tumeurs. Ils sont donc pleinement responsables du développement de la maladie. La compréhension de ces processus permet de mieux appréhender certaines des problématiques principales de la biologie du cancer.

**Origines et dynamique de l’hétérogénéité intra-tumorale** La grande majorité des tumeurs solides présente une très forte hétérogénéité génétique et phénotypique (Navin, Kendall, et al. 2011). Cette hétérogénéité apparaît dès la cancérogenèse et se poursuit jusqu’à la métastase (Maley, Galipeau, Finley, et al. 2006; Navin, Krasnitz, et al. 2010). Généralement, les tumeurs les plus hétérogènes sont également les plus agressives, et la survie est plus faible chez les patients concernés (Maley, Galipeau, Finley, et al. 2006; Marusyk and Polyak 2010; Mroz et al. 2015). L’émergence de cette hétérogénéité peut facilement s’expliquer par la création de nouveaux génotypes et phénotypes au cours de l’évolution clonale et de la plasticité phénotypique (L. L. Campbell and Polyak 2007; Shackleton et al. 2009). Néanmoins, son maintien au cours de l’évolution de la tumeur est particulièrement difficile à envisager.

Concernant la diversité génétique, l’interférence clonale et la compétition entre variants possédant des mutations avantageuses devraient défavoriser la co-existence de nombreux génotypes (Iwasa and Michor 2011). Cette diversité ne devrait être constituée que de mutations neutres, et ne pourrait donc être maintenue de manière stable au cours du temps. Néanmoins, ainsi que cité plus haut (section 2.2), plusieurs phénomènes écologiques viennent modifier cette dynamique évolutive : l’adaptation locale dans les tumeurs spatialement hétérogènes d’une part, et la sélection fréquence-dépendante dans les réseaux d’interactions d’autre part.

Concernant la diversité phénotypique, la capacité proliférative des cellules souches cancéreuses est bien plus élevée que celle des cellules cancéreuses différenciées. La sélection naturelle devrait donc favoriser les cellules cancéreuses qui ne se différencient pas. Néanmoins, les cellules différenciées assurent des fonctions que les cellules souches n’assurent pas au sein de la tumeur, et les interactions entre ces

deux types cellulaires sont donc nécessaires à la survie des cellules souches cancéreuses (Sprouffske, Aktipis, et al. 2013).

**Dynamique de la récurrence cancéreuse** Suite à un traitement anti-cancéreux, on estime que le patient est en *rémission* lorsque son état s'améliore, voire lorsqu'il ne présente plus aucun symptôme de cancer. Néanmoins, rémission n'est pas guérison, dans la mesure où une tumeur peut se reformer entièrement plusieurs années après la disparition des symptômes. Cette *récurrence cancéreuse* se produit lorsque certaines cellules cancéreuses n'ont pas été éradiquées par la thérapie.

Plusieurs processus éco-évolutifs sont en mesure d'expliquer l'émergence d'une récurrence post-thérapeutique, au premier rang desquels se trouvent l'hétérogénéité des tumeurs. En effet, la plupart des tumeurs sont difficiles d'accès pour une administration locale, ce qui fait que de nombreuses molécules chimiothérapeutiques sont délivrées par voie générale (intraveineuse) ou entérale (orale). Les cellules cancéreuses les plus exposées aux molécules cyto-toxiques/-statiques sont celles situées aux abords des vaisseaux sanguins, tandis que la faible diffusion au sein de la tumeur préservera les cellules les plus éloignées (Alfarouk, Ibrahim, et al. 2013) : c'est une des raisons pour lesquelles la résection est toujours appliquée en première intention lorsqu'elle est possible. De même, les conditions abiotiques de la tumeur (l'acidose, notamment) sont capables de partiellement inactiver les molécules chimiothérapeutiques, et donc de diminuer encore l'exposition des cellules cancéreuses les plus éloignées (Gatenby and R. J. Gillies 2004). De plus, la chimiothérapie est un stress toxique élevé et transitoire, et donc une pression de sélection sur les cellules cancéreuses. L'hétérogénéité phénotypique d'une tumeur participe donc à la récurrence : la probabilité qu'au moins une cellule augmente en fréquence dans la population sous une pression de sélection est d'autant plus forte que la variabilité phénotypique est élevée (Frédéric Thomas, Ujvari, Gidoin, et al. 2017).

En outre, la chimiothérapie module les interactions biologiques entre cellules cancéreuses, d'une manière qui favorise la récurrence. En effet, en augmentant massivement la mortalité dans les populations de cellules cancéreuses, la chimiothérapie procède à un relâchement de la compétition (*competitive release*, Enriquez-Navas, Wojtkowiak, and Gatenby 2015) sur les cellules survivantes : ces cellules peuvent proliférer sans être limitées par d'éventuels compétiteurs. Une augmentation rapide de la prolifération cellulaire, après un cycle de chimiothérapie, peut également être favorisée par la coopération entre cellules souches cancéreuses (Kurtova et al. 2015), voire même par la coopération de cellules cancéreuses mortes durant la chimiothérapie (Ford et al. 2015).

### 3 Impacts écologiques et évolutifs du processus cancéreux

L'interface de la biologie du cancer et des sciences de l'évolution s'est longtemps concentrée sur une explication évolutionniste du processus cancéreux. Il est ainsi possible d'expliquer comment cette pathologie progresse durant la vie d'un individu, selon une dynamique éco-évolutive. Néanmoins, cancer et évolution biologique interagissent à de plus grandes échelles de temps et de populations : le cancer interagit avec l'écologie et l'évolution des espèces. Ainsi, d'une part, le cancer, comme tout processus biologique, possède une origine évolutive qui peut être retrouvée dans la phylogénie. D'autre part, la caractérisation des impacts écologiques et évolutifs du cancer a été particulièrement pauvre jusqu'ici.

#### 3.1 Le cancer dans l'arbre de la vie

**Ubiquité et omnitemporalité du cancer** Si la lignée humaine semble avoir toujours été affectée par le cancer, cette pathologie existe depuis bien plus longtemps. En effet, le registre fossile du Jurassique

comporte plusieurs cas de tumeurs retrouvées dans des ossements de Dinosaures (p. ex. Rothschild, Tanke, et al. 1998; Rothschild, Witzke, and Hershkovitz 1999), avec une incidence comparable à celle observée de nos jours (Natarajan et al. 2007). Ces découvertes, bien qu'éparses, permettent d'identifier le cancer comme une pathologie ancienne, présente chez les Amniotes depuis au moins 150 millions d'années. Cependant, le cancer semble être répandu parmi tout le règne animal, puisque des cas ont été observés chez d'autres Chordés (Albert C Smith 2000), d'autres Deutérostomiens (A C Smith et al. 1973), d'autres Bilatériens (Schaeffer 1993), et d'autres Métazoaires (Peters, Halas, and McCarty 1986). En dehors des Métazoaires, le cancer est connu chez les Eumycètes (Dorn 1970), les Chlorobiontes (Braun 1978) et les Straménopiles (Apt 1988). Si le cancer semble donc être universellement répandu parmi les organismes multicellulaires (Aktipis, Boddy, Jansen, et al. 2015), des taxons unicellulaires eux-mêmes semblent risquer le développement de néoplasies (Chromalvéolés et Euglénozoaires, Lun et al. 2015).

**Origines évolutives du cancer** Le cancer est une pathologie ancienne, et largement répandue parmi l'ensemble des grands règnes multicellulaires : cela pourrait indiquer que le cancer est un phénomène inhérent à la multicellularité. En effet, les gènes liés à la protection contre le cancer (*gatekeepers* et *caretakers*) sont apparus au moment de la divergence des Métazoaires (Domazet-Loso and Tautz 2010) : l'évolution de ces caractères indique que le cancer est apparu peu de temps après l'émergence (voire en même temps) des premiers organismes multicellulaires.

L'origine de la multicellularité se situe dans l'association d'organismes unicellulaires (John Maynard Smith and Szathmáry 1995). Cette transition majeure suppose que l'association soit permanente et stable dans le temps : ceci n'est possible qu'à condition que les différentes cellules aient un intérêt commun, qui est peut être réalisé par la spécialisation de lignées cellulaires pour favoriser le partage des fonctions biologiques (p. ex. métabolisme nitrogénique des hétérocystes chez *Nostoc sp.*, Fleming and Haselkorn 1973). Les associations temporaires d'organismes unicellulaires (chez les Amoebozoaires, cf. Strassmann, Zhu, and Queller 2000 ; les Eumycètes, cf. Smukalla et al. 2008 ; les Eubactéries, cf. Dunny, Brickman, and Dworkin 2008 ; et les Archées, cf. Sowers, Boone, and Gunsalus 1993) ne sont stables que lorsque les coûts et les bénéfices de l'interaction sont partagés par tous les partenaires (si le partage est aléatoire, il doit être non biaisé). En effet, le risque d'une interaction coopérative est que l'un des partenaires cesse de porter les coûts de l'interaction, tout en profitant des bénéfices (comportement *tricheur*). L'apparement entre cellules participe à diminuer le potentiel d'émergence de tricheurs au sein des communautés de cellules (Gilbert et al. 2007; R E Michod and Roze 2001). De même, lorsqu'un type cellulaire est spécialisé dans la reproduction, les associations multicellulaires sont stabilisées lorsque le mode de reproduction est équitable dans l'apparement des gamètes/propagules à la lignée somatique (R E Michod and Roze 2001). Ainsi, une coordination entre cellules somatiques et germinales d'un même organisme est nécessaire à la stabilité des bénéfices de leur association.

Nous avons vu précédemment (section 2.1) que la cellule cancéreuse est une unité de sélection à part entière. Il s'agit donc de l'émergence de lignées unicellulaires à partir de lignées multicellulaires. Celle-ci est possible si les adaptations développées pour favoriser la multicellularité sont réprimées, et si les anciennes adaptations héritées d'ancêtres unicellulaires sont sur-exprimées. Cela semble être le cas chez les cellules cancéreuses (Trigos et al. 2017) : ainsi, leurs gènes perdent leurs fonctions pour ceux propres aux organismes multicellulaires (*caretakers* et *gatekeepers*, cf. Domazet-Loso and Tautz 2010), et en gagnent pour ceux hérités d'organismes unicellulaires (proto-oncogènes, cf. Watari et al. 2010). Ce retour évolutif à l'état unicellulaire n'est néanmoins pas stable dans le temps puisque ces lignées sont vouées à s'éteindre avec leur organisme d'origine (Arnal, Ujvari, et al. 2015, mais voir Ujvari, Gatenby, and Frédéric Thomas 2016 pour des cas de cancers transmissibles). Néanmoins, un retour à l'état uni-

cellulaire à partir de lignées multicellulaires, qui soit stable sur des millions d'années, a déjà été observé (ex. des Myxozoaires au sein des Métazoaires, Smothers et al. 1994).

**Existe-t-il des espèces dépourvues de cancer ?** Le cancer semble être universellement répandu chez les organismes multicellulaires. Des phénomènes similaires au cancer ont même été observés dans des taxons unicellulaires : Amoebozoaires, Chromalvéolés, Euglénozoaires, Eubactéries et Archées (Lun et al. 2015; Sowers, Boone, and Gunsalus 1993; Strassmann and Queller 2011; Velicer, Kroos, and Lenski 2000). Néanmoins, aucun processus similaires au cancer n'a jamais été observé dans certains taxons, pourtant multicellulaires : notamment chez les Hémichordés, Placozoaires, Porifères et Cténophores (Aktipis, Boddy, Jansen, et al. 2015). Il est évidemment à noter que cette absence actuelle d'observation peut n'être que temporaire : ainsi, le cancer est tellement rare chez le rat-taube glabre *Heterocephalus glaber* que le premier cas n'a été observé qu'en 2016, et en captivité (Delaney et al. 2016). Toutefois, tous les taxons touchés par le cancer ne le sont pas de la même manière. Au sein des Métazoaires, les prévalences peuvent varier de moins de 1% jusqu'à plus de 60% des individus touchés, selon les espèces (Madsen et al. 2017). De même, les végétaux sont particulièrement épargnés par le cancer (Doonan and Sablowski 2010), et la plupart des cas observés sont d'origine infectieuse (C.-W. Lee et al. 2009) ou embryonnaire (Gaspar et al. 1991). Si le cancer est un phénomène inhérent à la coopération entre cellules, l'histoire évolutive de chaque taxon peut donc nous renseigner sur les variations de ce phénomène au sein du vivant.

### 3.2 Le cancer comme pression de sélection

**L'évolution des défenses au cancer** Le cancer est associé à de nombreuses modifications phénotypiques chez les organismes multicellulaires : ces modifications sont d'ordre métabolique (Tisdale 2002), physiologique (Almand et al. 2001; J. Huang et al. 2016), voire comportemental (Davidson et al. 2002; Lowery 2015). Ces modifications phénotypiques sont globalement associées à une plus forte mortalité (Chaloupka, Balazs, and Work 2009; Ciocan, J. D. Moore, and Rotchell 2006; Martineau et al. 2002) et/ou une plus faible fertilité (Domazet-Loso, Klimovich, et al. 2014; Shimonohara et al. 2013) des individus. Le cancer est donc une source de réduction de la valeur sélective individuelle.

Pour réduire la contrainte exercée par le cancer, de nombreuses adaptations ont été développées, à plusieurs niveaux (DeGregori 2011; Harris, Schiffman, and Boddy 2017). Ainsi, au niveau de la cellule, les mécanismes de réparation de l'ADN, les points de contrôle du cycle cellulaire et l'apoptose filtrent la grande majorité des mutations somatiques. De même, le raccourcissement progressif des télomères à chaque division empêche une lignée cellulaire de se diviser indéfiniment. Au niveau des tissus, seules certaines cellules sont capables de se diviser (cellules souches uni- et multi-potentes chez l'adulte), limitant ainsi le nombre de cellules capables de se transformer. De plus, l'inhibition de contact empêche l'invasion des cellules cancéreuses, en déclenchant l'apoptose de toute cellule qui romprait son attachement aux cellules adjacentes. Enfin, la surveillance immunitaire élimine toute cellule présentant des récepteurs de surface aberrants (Koebel et al. 2007).

Si la majorité de ces mécanismes sont présents chez tous les Métazoaires, il existe de fortes variations entre espèces pour l'intensité de ces mécanismes. Ainsi, une expression plus forte de ces mécanismes peut être sélectionnée dans des espèces davantage exposées au cancer, de par une vie plus longue et/ou un nombre de cellules plus important : c'est le cas chez l'éléphant *Elephas maximus*, dont les (au moins) 20 copies du *gatekeeper p53* réduisent considérablement le risque de cancer dans cette espèce (Abeglen et al. 2015). De même, une expression plus forte de ces mécanismes peut être sélectionnée chez les espèces et/ou dans les périodes où l'impact du cancer est le plus important sur la valeur sélective :

par exemple, durant le développement et durant la période de fertilité (DeGregori 2011; Foo, Leder, and Michor 2011).

**Le cancer est-il une pression de sélection importante ?** L'existence même de nombreux mécanismes de défense face au cancer prouve qu'il s'agit d'une pression de sélection sur les organismes. Les conséquences d'une perte de fonction de l'un ou plusieurs de ces mécanismes (c'est à dire un fort risque de cancer) affecte de manière considérable le phénotype et la valeur sélective d'un individu. De même, la sur-activation de ces mécanismes est susceptible d'être néfaste à l'organisme (p. ex. Campisi 2001). On peut donc s'attendre à ce que les défenses contre le cancer soient actuellement sous sélection stabilisante.

Toutefois, ce n'est pas parce que l'évolution des défenses contre le cancer est limitée que le cancer représente une pression de sélection. L'impact du cancer sur l'écologie et l'évolution des espèces pourrait, en fait, être particulièrement restreint. En effet, les défenses anti-cancer sont exprimées principalement en début de vie, et tendent à décliner lors de la sénescence (p. ex. Pawelec, Derhovanessian, and Larbi 2010). Si le cancer ne se manifeste qu'à partir de la sénescence, il n'aura aucun impact sur la fécondité des individus, et ne devrait donc pas constituer une pression de sélection. De même, certaines espèces expriment très peu de défenses face au cancer : 42% des individus expriment un cancer dans les populations captives de souris *Mus musculus* (Andervont and T. B. Dunn 1962). Dans les écosystèmes naturels, de telles espèces sont peu exposées au cancer car elles meurent souvent de causes externes (telles que la prédation) avant que le cancer n'ait eu le temps de se développer.

Il est toutefois à noter que le cancer est une pathologie dont le développement se déroule sur une grande échelle de temps par rapport à la vie de l'individu. Si la majorité des symptômes connus du cancer émergent en fin de vie, il est certain que les impacts du cancer sur le phénotype restent inconnus pour des stades moins avancés (Marion Vittecoq et al. 2013). Il est par exemple possible que certains phénotypes associés au cancer ne soient pas la cause mais la conséquence du processus cancéreux (voir Frédéric Thomas, Rome, et al. 2017 pour le comportement alimentaire). L'impact du cancer sur l'évolution des organismes, et particulièrement son impact sur la valeur sélective individuelle, reste donc une question en suspens.

**Plasticité phénotypique et réactions au cancer** Il est à noter que, face à la menace du cancer, la suppression n'est pas la seule réponse évolutive possible. En effet, certaines modifications plastiques de la physiologie et du comportement participent à restreindre les impacts du cancer sur la valeur sélective une fois que celui-ci est déjà installé (Ujvari, Beckmann, et al. 2016; M Vittecoq et al. 2015). Ces modifications plastiques peuvent directement avoir pour fonction de ralentir la progression cancéreuse : les chimpanzés *Pan troglodytes* consomment des plantes connues pour leurs propriétés anti-tumorales (Masi et al. 2012), et l'augmentation précoce des interactions sociales conspécifiques ralentit la progression cancéreuse chez les mouches *Drosophila melanogaster* (Dawson et al. 2017). Au contraire, ces modifications plastiques peuvent avoir pour fonction de maximiser la fécondité à court terme en dépit du cancer. C'est ce qui a été observé chez *D. melanogaster* où les femelles cancéreuses atteignent plus tôt leur pic de ponte (Arnal, Jacqueline, et al. 2017), et chez les diables de Tasmanie *Sarcophilus harrisii* dont le régime de reproduction est passé d'itérofaire à sémelpare sous la pression d'un cancer transmissible (M. E. Jones et al. 2008).

### 3.3 Le cancer dans les écosystèmes

**De l'importance du contexte écologique** Si le cancer est la cause d'adaptations visant à diminuer cette source de réduction de la valeur sélective, l'interaction avec d'autres processus écologiques peut



réguler l'évolution des défenses et des susceptibilités au cancer. En effet, le contexte écologique peut, en premier lieu, moduler les impacts du cancer sur la valeur sélective individuelle. Comme cité plus haut (section 3.2), les espèces les plus massives et vivant le plus longtemps (telles que l'éléphant, Abegglen et al. 2015) présentent généralement davantage de résistances au cancer, car leur risque de cancer est plus élevé. De même, des espèces vivant moins longtemps et/ou exposées à d'autres sources de mortalité (telles que la souris, Andervont and T. B. Dunn 1962) présentent moins de résistances au cancer, car le cancer représente une pression de sélection négligeable pour elles. Pour ces dernières, la compétition intraspécifique est généralement élevée (du fait d'un temps de génération court), et l'allocation des ressources à la reproduction diminue également l'expression de mécanismes de défenses contre le cancer (Boddy et al. 2015). En outre, si la sélection de défenses anti-cancer s'arrête généralement à la fin de la période reproductive, elle peut se poursuivre en période post-reproductive dans des espèces où une part significative des soins aux individus apparentés sont prodigués durant cette période (maximisant ainsi la valeur sélective inclusive, J. S. Brown and Aktipis 2015).

Par ailleurs, la sélection sur les caractères liés à la résistance ou à la susceptibilité au cancer peut être modulée par des mécanismes de pléiotropie et/ou d'autres pressions de sélection. En effet, l'allèle oncogène du proto-oncogène *xmrk* (mélanome) est favorisé par sélection sexuelle chez les mâles du poisson *Xiphophorus sp.*, du fait d'une plus grande taille chez les individus porteurs (Fernandez and Bowser 2010). De même, les allèles oncogènes des caretakers *brca1/2* (cancers mammaires et ovariens) pourraient se maintenir dans les populations humaines par un processus de pléiotropie antagoniste : les porteuses de ces allèles semblent en effet avoir une fécondité plus forte que la moyenne (K. R. Smith et al. 2012). En outre, une partie des défenses anti-cancer peut provenir de l'exaptation de caractères sélectionnés pour d'autres fonctions : par exemple, l'apoptose semble avoir été sélectionnée comme défense anti-virale en premier lieu (Krakauer and Payne 1997).

**Une source de mortalité comme les autres ?** Dans de nombreuses espèces, le cancer n'est pas la source principale de mortalité : les accidents, les pénuries de ressources, la prédation, et d'autres pathologies (infectieuses notamment) peuvent davantage menacer la survie individuelle que le cancer lui-même. Néanmoins, le processus cancéreux affaiblit les organismes qu'il touche, et cette diminution de la vigueur pourrait rendre un individu plus susceptible à ces autres sources de mortalité (Roche, Anders P Møller, et al. 2017; Marion Vittecoq et al. 2013). Ainsi, l'immuno-suppression (Almand et al. 2001; Wolf et al. 2003) et la réallocation des ressources à la fécondité à court terme (Arnal, Jacqueline, et al. 2017; M. E. Jones et al. 2008) chez les individus cancéreux pourraient les rendre plus susceptibles aux maladies infectieuses. De même, la diminution de la vigueur pourrait renforcer le risque de prédation et diminuer la compétitivité (comme observé chez les individus parasités, Anders P Møller and Nielsen 2007). De nombreux effets potentiels du cancer dans les écosystèmes sont prévisibles, mais ont rarement été observés jusqu'ici : cela peut être dû au fait que les individus cancéreux seraient rapidement éliminés par ces autres sources de mortalité (Marion Vittecoq et al. 2013).

**Cancer et biologie de la conservation** Le cancer, en tant que source (directe ou indirecte) de mortalité, représente un enjeu majeur en biologie de la conservation. Si la plupart des espèces ont toujours été exposées au cancer et ont pu s'y adapter, de nouvelles pressions carcinogéniques peuvent apparaître rapidement et menacer espèces et communautés (McAloose and Newton 2009). Du fait de l'augmentation récente de la pollution carcinogénique, la morbidité liée au cancer a explosé durant les dernières années dans certaines communautés (Ellegren et al. 1997; Martineau et al. 2002; A P Møller, Bonisoli-Alquati, and T A Mousseau 2013). Dans la faune sauvage de Tchernobyl (Ukraine), de nombreuses espèces d'oiseaux et d'invertébrés ont décliné en abondance et en diversité sous l'effet de la radioactivité (A P

Møller and T A Mousseau 2007a,b; Anders P Møller and Timothy A Mousseau 2009).

Une des menaces les plus fortes actuellement exercées par le cancer est la tumeur faciale transmissible du Diable de Tasmanie. Cette pathologie se transmet horizontalement par morsure, et progresse rapidement jusqu'à la métastase. La transmission de ce cancer est particulièrement difficile à contrôler, dans la mesure où la plupart des accouplements se soldent par des morsures (Wells et al. 2017). Depuis sa découverte en 1996, la population naturelle de *S. harrisii* a décliné de 90%, dont la majeure partie est imputable au cancer (McCallum 2008; McCallum et al. 2009). Si les cancers transmissibles ont longtemps été considérés comme rares, il semblerait qu'ils soient beaucoup plus communs chez les invertébrés marins, avec des possibilités de transmission inter-espèces (Metzger, Reinisch, et al. 2015; Metzger, Villalba, et al. 2016). Néanmoins, plusieurs espèces semblent avoir contrôlé, voire éliminé cette pathologie (Metzger, Villalba, et al. 2016; Murchison et al. 2014), et l'impact du cancer sur les populations de *S. harrisii* pourrait être une exception plutôt qu'une généralité.

## 4 Le cancer, un processus à l'interface de plusieurs échelles

Le cancer est un objet en évolution (au sein de chaque organisme, section 2), mais c'est également le produit d'une évolution (celle des organismes multicellulaires, section 3.1), qui influence l'évolution des organismes (section 3.2). Comprendre les implications du processus cancéreux dans leur globalité nécessite donc d'aborder les différentes unités de sélection qui sont impliquées dans son (ou ses) évolution(s). Les cellules cancéreuses interagissent de manière réciproque avec leur micro-environnement, et donc les unes avec les autres, contraignant ainsi l'évolution de la tumeur en tant que groupe : ce point sera abordé dans la partie II (voir Fig. 1A). Les cellules cancéreuses réduisent la fécondité et la survie de l'organisme, mais certains contextes écologiques peuvent réduire la contrainte qui pèse sur l'évolution des susceptibilités au cancer : ce point sera abordé dans la partie III (voir Fig. 1B). Plus globalement, le cancer et l'organisme sont impliqués dans des interactions réciproques, tantôt le cancer manipulant l'organisme à son avantage et tantôt l'organisme se défendant contre la prolifération cellulaire incontrôlée : ce point sera abordé dans la partie IV (voir Fig. 1C).

Aussi, la section suivante présente l'état des connaissances sur les interactions entre les différentes échelles auxquelles le cancer est impliqué. Ces échelles n'interagissent pas toutes entre elles aux mêmes échelles de temps et d'espace ; mais comprendre le cancer nécessite de passer de la cellule à l'individu, de l'individu à la population, et de la population aux différentes lignées qui forment le vivant.

### 4.1 Cancer, conflits, et compromis

**Entre communautés de cellules** Au sein de chaque organisme, chaque cellule peut être abordée comme une unité de sélection. La plupart de ces cellules ont évolué vers un même intérêt – la reproduction de la lignée germinale –, et coopèrent donc à assurer l'homéostasie de l'organisme. Néanmoins, une partie des cellules de l'organisme, les cancéreuses, peut favoriser sa propre reproduction individuelle au détriment de celle des autres. Cellules cancéreuses et non cancéreuses ne partagent donc pas le même intérêt évolutif. De ce conflit résultent des interactions antagonistes entre ces deux communautés. L'évolution des cellules cancéreuses favorise donc celles qui excluent spatialement les cellules non cancéreuses (par mise en place de conditions défavorables, Carmona-Fontaine et al. 2013), qui les excluent compétitivement (par consommation des ressources vitales, Chang et al. 2015), ou qui les exploitent (par détournement des fonctions physiologiques, Lambert et al. 2011). Le potentiel d'adaptation des cellules non cancéreuses en réponse à l'évolution des cellules cancéreuses est limitée, notamment par les faibles nombres de génération et par la réparation de l'ADN (à l'exception du système immunitaire adaptatif).

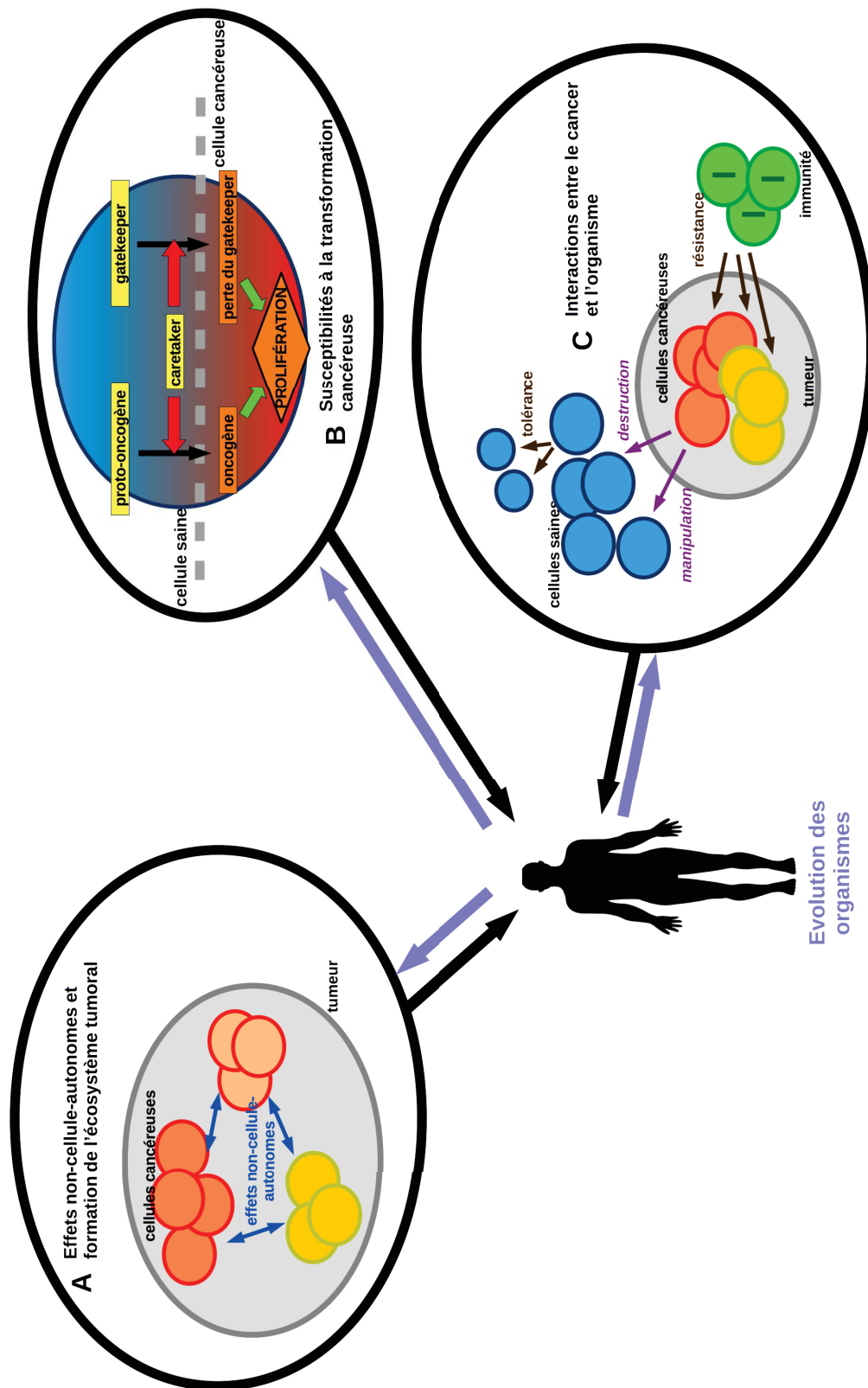


Figure 1 – Thématiques explorées au sein de cette thèse. (A) Ecologie et évolution intra-tumorales (partie II) ; (B) Le cancer comme pression de sélection (partie III) ; et (C) Des tumeurs aux populations (partie IV).

En revanche, à l'évolution d'une lignée de cellules cancéreuses peut répondre l'évolution d'autres lignées de cellules cancéreuses. Chaque cellule est une unité de sélection, et la mise en place d'une sélection de parentèle au sein d'une tumeur peut être limitée par l'instabilité génomique et le faible temps d'évolution des cellules cancéreuses (Arnal, Ujvari, et al. 2015). Il en résulte donc une forte compétition entre cellules cancéreuses, par exploitation ou par interférence (voir section 2.2). Il semblerait également que différentes tumeurs puissent être en conflit les unes avec les autres au sein d'un même organisme (Ebos et al. 2009).

**Entre le cancer et l'organisme** A l'exception des cas anecdotiques de cancers transmissibles, les cellules cancéreuses et leur organisme-hôte meurent généralement au même moment : soit du fait du processus cancéreux, soit d'une autre cause (Arnal, Ujvari, et al. 2015). La survie des cellules cancéreuses dépend donc de leur capacité à maintenir l'organisme en vie. Néanmoins, l'intérêt évolutif de chacune de ces unités de sélection réside dans sa reproduction, et non pas dans sa survie. Dans la mesure où les deux ne se reproduisent pas conjointement, les cellules cancéreuses sont donc en conflit avec l'organisme : la prolifération de ces cellules amoindrit la fécondité de leur hôte. Il en résulte donc une course aux armements entre les organismes et leurs cellules cancéreuses (Casás-Selves and DeGregori 2011) : les uns s'adaptent pour faire face à la prolifération anarchique, mais la sélection naturelle favorise chez les autres la capacité à contourner ces défenses (Gatenby and R. J. Gillies 2008).

Néanmoins, le potentiel d'évolution des organismes face à celle des cellules cancéreuses est limité par l'interaction avec d'autres processus écologiques (voir section 3.3). De même, le potentiel d'évolution des cellules cancéreuses face à celle des organismes est limité, par le fait que les cellules cancéreuses meurent avec l'organisme, et que l'évolution d'une lignée doit toujours partir d'une cellule non cancéreuse (Arnal, Ujvari, et al. 2015). En ce sens, les cancers transmissibles représentent un aboutissement de l'évolution du cancer : la transmission d'une lignée cancéreuse l'autorise à poursuivre son évolution au delà de la mort de son hôte (Ujvari, Gatenby, and Frédéric Thomas 2016).

## 4.2 Evolution intra-organisme, évolution inter-organisme

**Le cancer est un parasite** Les cellules cancéreuses survivent et se reproduisent aux dépens de l'organisme dont elles sont issues. C'est également le cas de toutes les autres cellules de l'organisme, mais ces dernières ont un intérêt commun. Au contraire, l'évolution des cellules cancéreuses génère une divergence suffisante avec les cellules de l'organisme (Adamek and Stoj 2014; Duesberg et al. 2011) pour les considérer comme des entités distinctes : les cellules cancéreuses exercent donc un comportement égoïste. Ainsi, de nombreux parallèles ont été effectués entre le fonctionnement du cancer et celui des communautés de micro-parasites. Globalement, on notera que les cellules cancéreuses, de même que les micro-parasites (Hamblin, P. A. White, and Tanaka 2014), sont capables de moduler leur micro-environnement d'une manière favorable à leur prolifération (*construction de niche*, Adamek and Stoj 2014; Lambert et al. 2011). Parmi de nombreux exemples, de même que les micro-parasites sont capables d'échapper (Sacks and Sher 2002) ou de supprimer (Duvaux-Miret et al. 1992) la réponse immunitaire, le processus cancéreux génère également ces phénomènes (Almand et al. 2001; Khong and Restifo 2002). En outre, l'organisation des communautés de cellules cancéreuses participe, de même que chez les micro-parasites, à l'évolution de la résistance aux molécules thérapeutiques (Ben-Jacob, Coffey, and Levine 2012; Lambert et al. 2011).

Les cancers transmissibles présentent également une diversité de modes de transmission similaire à celle des micro-parasites. Ainsi, des cellules cancéreuses peuvent se transmettre dans le milieu environnant (leucémies des bivalves, Metzger, Reinisch, et al. 2015), par contact sexuel (tumeur vénérienne transmissible canine, Murchison et al. 2014), par morsure (tumeur faciale transmissible du Diable de

Tasmanie, Hamede, McCallum, and M. Jones 2013), et même par des vecteurs (sarcome à cellules réticulaires contagieux du Hamster doré *Mesocricetus auratus*, Banfield et al. 1965). On notera également qu'un cancer peut se transmettre par voie placentaire (de nombreux cancers concernés, parmi lesquels des lymphomes, mélanomes, carcinomes hépatiques, etc., Tolar and Neglia 2003), et également d'un parasite à son hôte (tumeur pulmonaire humaine formée par des cellules du ténia nain *Hymenolepis nana*, Muehlenbachs et al. 2015).

**Le cancer est un sous-produit évolutif** Les cellules cancéreuses divergent génétiquement et phénotypiquement de l'homéostasie de l'organisme par mutation, dérive et sélection naturelle (voir section 2). Néanmoins, ces divergences sont *per se* le produit de l'évolution des organismes, et non seulement celle des cellules cancéreuses. Ainsi, les cellules cancéreuses surexpriment de nombreux caractères normalement exprimés durant le développement embryonnaire uniquement (Yaddanapudi et al. 2012), et des caractères hérités d'ancêtres unicellulaires (Trigos et al. 2017). Si ces caractères sont sélectionnés chez les cellules cancéreuses, ils l'ont également été dans les lignées pluricellulaires au préalable. Plus largement, on pourra remarquer que tous les caractères exprimés par les cellules cancéreuses sont : soit des caractères déjà encodés dans le génome et éventuellement détournés de leurs fonctions initiales (c'est à dire des exaptations) ; soit des caractères dérivés de caractères déjà encodés dans le génome. Par conséquent, l'évolution des cellules cancéreuses, contrairement à celle d'autres entités parasitaires, est nécessairement contingente à l'évolution des organismes dont elles dérivent (Frédéric Thomas, Ujvari, Renaud, et al. 2017).

Par ailleurs, l'évolution des organismes a produit un ensemble de conditions génétiques et microenvironnementales, qu'elles soient des défenses anti-cancer ou non (voir section 3.2). Pour qu'un cancer émerge, des cellules doivent nécessairement s'adapter à ces contraintes de manière séquentielle (Gatenby and R. J. Gillies 2008) : par exemple, la sélection naturelle favorise davantage les cellules dont les deux copies homologues d'un gatekeeper perdent leur fonction, que les cellules dont une seule copie est mutée. Eussent ces contraintes été différentes, les cellules cancéreuses n'émergeraient pas selon la même séquence et avec les mêmes caractéristiques. On a, par exemple, pu observer des métastases dans tous les taxons dotés d'un système circulatoire, mais jamais chez les organismes sans système circulatoire (Aktipis, Boddy, Jansen, et al. 2015).

D'une part, l'évolution des organismes produit donc une grande diversité de caractères dont les cellules cancéreuses exaptent de nouvelles fonctions ou dérivent de nouvelles structures. D'autre part, l'évolution des organismes génère également les contraintes auxquelles des cellules doivent répondre pour survivre et proliférer au sein d'un organisme. Le cancer est donc un sous-produit non adaptatif de l'évolution des organismes, et un symptôme du *bricolage* opéré par l'évolution biologique (Jacob 1977).

**Ce parasite qui ne coévolue pas** Plusieurs cas de cancers transmissibles existent dans le monde vivant, et la persistance de ces lignées sur des temps évolutifs (Murchison et al. 2014) peut autoriser à les qualifier de nouvelles espèces de micro-parasites. Les micro-parasites classiques peuvent se transmettre horizontalement et verticalement d'un hôte à l'autre : les adaptations développées durant l'évolution à l'intérieur d'un hôte donné peuvent donc se répandre dans les populations, et fonctionner contre d'autres hôtes. Les populations d'hôtes peuvent alors s'adapter en réponse aux changements phénotypiques des populations de parasites, lesquels en retour peuvent s'adapter à nouveau : ce processus de coévolution implique une sélection variable dans le temps, et une évolution permanente de chacun des partenaires en réponse aux changements des autres (J Maynard Smith 1976). On peut donc escompter que cette dynamique évolutive ait lieu dans le cas des cancers transmissibles, ce qui semble avoir lieu rapidement chez les diables de Tasmanie (Epstein et al. 2016).

Néanmoins, ces cas restent (pour le moment) anecdotiques parmi la diversité des taxons concernés par le cancer. Dans la grande majorité des cas, les cellules cancéreuses vivent et interagissent effectivement avec les organismes selon un mode parasitaire, mais leur évolution ne suit pas la même dynamique. Les cellules cancéreuses émergent en contournant les défenses anti-cancer sélectionnées chez les organismes : elles s'adaptent donc en réponse à l'évolution de leurs hôtes. Néanmoins, les cellules cancéreuses meurent avec leur hôte, et l'évolution d'une lignée cancéreuse doit toujours démarrer d'une lignée saine, et se ré-adapter à son organisme (Arnal, Ujvari, et al. 2015). Il ne s'agit donc pas d'une co-évolution, car les adaptations partagées par différentes lignées de cellules cancéreuses (Hanahan and Weinberg 2011) sont le résultat de convergences évolutives. Néanmoins, il n'est pas certain que le cancer soit, tel Sisyphé, condamné à perdre la course aux armements avec les organismes. D'une part, l'évolution des défenses anti-cancer est limitée ; d'autre part, toute nouvelle adaptation (liée ou non aux défenses anti-cancer) de la part des organismes pourrait être exaptée par les cellules cancéreuses... réclamant ainsi de nouvelles adaptations de la part des organismes.

## Partie II

# Écologie et évolution intra-tumorales

Décrire et comprendre la dynamique évolutive d'un phénomène requiert de connaître l'origine des variations génétiques phénotypiques, et les effets de ces variations sur la survie et la fécondité des individus. Ces effets peuvent varier du tout au tout selon le contexte dans lequel ils sont placés : un caractère peut avoir un effet bénéfique dans un environnement, et néfaste dans un autre. Cette dynamique peut être encore complexifiée, si l'on considère les interactions que chaque individu entretient avec son environnement : en modifiant l'environnement, un individu peut non seulement modifier ses propres survie et fécondité, mais également celle d'autres individus. Une approche écologique est donc essentielle à la compréhension de nombreuses dynamiques évolutives.

C'est également le cas de l'évolution intra-tumorale. La génomique du cancer a globalement classé les mutations selon qu'elles ont un effet bénéfique ou non sur la prolifération des cellules cancéreuses : les mutations et gènes *drivers* accélèrent la croissance tumorale, les mutations et gènes *passengers* non. Néanmoins, cette classification n'inclut pas de manière explicite les effets de ces mutations sur l'écologie de la tumeur. Ce manque restreint la compréhension de la progression cancéreuse pour plusieurs raisons. D'une part, la prolifération cellulaire incontrôlée ne dépend pas uniquement de la dérégulation génétique, mais repose beaucoup sur la permissivité du micro-environnement (Tabassum and Polyak 2015) : les interactions avec le micro-environnement sont donc un *driver* à part entière de la progression cancéreuse. D'autre part, les régimes de sélection varient fortement d'un endroit à l'autre de la tumeur et au cours du temps (Swanton 2012) : un même variant peut donc proliférer ou s'éteindre, selon l'endroit et le moment où ce variant apparaît.

Aussi, dans ce chapitre, je propose une approche écologique pour décrire l'évolution des tumeurs : diviser les mutations, non uniquement selon qu'elles ont un effet bénéfique sur la prolifération, mais aussi selon qu'elles modifient le phénotype de cellules qui ne portent pas ces mutations. Ainsi, les mutations qui n'agissent que sur le phénotype des cellules qui les portent ont des effets *cellule-autonomes*. Les mutations qui sont également capables d'agir sur le phénotype d'autres cellules ont des effets *non-cellule-autonomes*. Dans un premier temps, je passe en revue l'ensemble des mécanismes par lesquels une mutation peut avoir un effet non-cellule-autonome, et l'ensemble des conséquences évolutives des mutations, selon qu'elles ont des effets cellule-autonomes ou non-cellule-autonomes (section 5). Dans un second temps, j'expose un modèle d'évolution branchante dans lequel je fais varier la fréquence des mutations à effets non-cellule-autonomes, de sorte à tester si ces mutations favorisent effectivement la diversité clonale au sein des tumeurs, comme suggéré par plusieurs publications (section 6).

## 5 Mutations et structure écologique des tumeurs

**Titre :** *Do cell-autonomous and non-cell-autonomous effects drive the structure of tumor ecosystems?*

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## Review

# Do cell-autonomous and non-cell-autonomous effects drive the structure of tumor ecosystems?



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## ABSTRACT

By definition, a driver mutation confers a growth advantage to the cancer cell in which it occurs, while a passenger mutation does not: the former is usually considered as the engine of cancer progression, while the latter is not. Actually, the effects of a given mutation depend on the genetic background of the cell in which it appears, thus can differ in the subclones that form a tumor. In addition to cell-autonomous effects generated by the mutations, non-cell-autonomous effects shape the phenotype of a cancer cell. Here, we review the evidence that a network of biological interactions between subclones drives cancer cell adaptation and amplifies intra-tumor heterogeneity. Integrating the role of mutations in tumor ecosystems generates innovative strategies targeting the tumor ecosystem's weaknesses to improve cancer treatment.

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## 1. Introduction

The transformation of healthy cells into malignant cells during carcinogenesis is a multistep process that involves the accumulation of genetic and epigenetic mutations [1], some of which conferring to the cells a higher proliferation rate [2] or any other hallmarks of cancers [3]. These cells develop at the expense of the host organism, switching from an altruistic to a selfish phenotype by a process of Darwinian somatic evolution [4]. Among the genetic mutations that accumulate in the transformed cells, some promote the malignant clone expansion and are commonly called “drivers”, whereas others have no effect on the malignant clone evolution and these neutral mutations are called “passengers” [5–7]. While expanding, tumors usually become heterogeneous [8–11]. The cellular phenotype, cytogenetic aberrations, genetic variants and epigenetic features progressively diverge. This tumor cell heterogeneity, which correlates with clinical progression [12], increases the probability that some tumor cells gain resistance to cancer therapies [13]. Tumor cell heterogeneity has been related to the occurrence of additional genetic mutations that define sub-clones [10,14]. This heterogeneity suggests that, at some time-point, the clonal dominance induced by the continuous accumulation of driver mutations in a tumor cell clone [15] is overcome by other factors that promote tumor cell diversity.

Facing tumor evolution as an ecological process may provide an explanation to a part of tumor heterogeneity [13], as microenvironmental constraints participate to shaping tumor organization during cancer progression [13,16]. Cancer cells and their microenvironment can be considered as a system, with natural selection promoting cell phenotypes that are highly competitive in a given, supportive microenvironment, and eliminating the phenotypes that are not competitive in that specific environment [16]. The common binary classification of driver and passenger mutations does not consider this ecological process in the dynamics of tumor evolution [17], *i.e.*, does not consider the combination of cell-autonomous and non-cell-autonomous effects [18,19].

Cell-autonomous effects (henceforth referred to as “CA effects”) are the properties conferred to a cell by the accumulation of genetic and epigenetic alterations. But these alterations can also affect the phenotypes of other cells through non-cell-autonomous effects (henceforth “NCA effects”): these remote effects can involve either direct cell–cell interactions or changes in the microenvironment (ME) [20]. In other words, cancer cells can overcome tumor ME constraints not only through the cell-autonomous effects of their mutations, but also through non-cell-autonomous effects that can affect the surrounding ME, including other cells. Cell-autonomous and non-cell-autonomous effects cooperate to generate the tumor cell phenotype, from cancer initiation to tumor progression and dissemination [21–25]. The ability of the ME to affect the consequences of genetic and epigenetic alterations that accumulate in a given cell overcomes the driver/passenger classification of mutations [25–28]. Thus, considering both cell-autonomous and non-cell-autonomous effects may describe more precisely and completely the evolutionary dynamics of cancer.

We herein discuss the contribution of CA and NCA effects to the generation of intra-tumor heterogeneity and their impact on cancer progression, then speculate about novel therapies that may be able to manipulate tumor ecosystem to eradicate all the tumor cells and cure the patients.

## 2. Cancer cells shape their microenvironment

Genetic and epigenetic mutations accumulate in cancer cells and are transmitted during cell divisions. CA effects only impact the phenotype of cells carrying the involved mutations, therefore intracellular mechanisms (or extracellular mechanisms at very local scale) are mainly involved in the process. They may have limited impact on the structure of tumors. Conversely, NCA effects trigger interactions both between

distant cells and between cells and their ME, which potentially impact tumor structure.

### 2.1. Diffusible messengers

The release of diffusible messengers, including peptides, nucleic acids and microvesicles, by tumor cells can trigger phenotypic changes, including morphologic, transcriptomic, proteomic and metabolomic changes, in other cells. NCA effects can consist of the release of growth factors acting in a paracrine manner on other cells to modulate tumorigenicity. This was experimentally demonstrated *in vivo* by showing that fibroblast growth factor (FGF) producing cells could increase the tumorigenicity of cells that do not produce FGF in a given tumor [29]. NCA effects can consist of the release of diffusible molecules that, in addition to promoting tumorigenesis [30], facilitate cancer recurrence [31]: *e.g.*, the release of PGE2 can promote the recruitment of cancer stem cells in the tumor [31]. NCA effects can also affect surrounding cells through RNA interference when miRNAs are released in tumor-cell derived microvesicles called exosomes [32] and instigate a tumorigenic phenotype in their ME, *e.g.*, by recruiting cancer-associated fibroblasts [33,34]. Whatever the molecules released, NCA effects often involve the recruitment of stromal cells to promote angiogenesis [35, 36], of fibroblasts to generate a matrix [37,38], of innate immune cells such as M2-polarized macrophages that create a pro-tumorigenic environment [39,40], just to list a few examples. In turn, stromal cells release their own diffusible signals that promote tumor cell growth and amplify the tumorigenic activities of NCA effects [41,42]. The signals sent to surrounding stromal cells can recruit them in order to create a community of highly-specialized cells able to sustain the metabolic needs of cancer cells [43–46]. Due to NCA effects, cancer and stromal cells therefore engage in a crosstalk that enhances tumor progression.

### 2.2. Vascularization and extracellular matrix

Vascularization is a key parameter of the tumor ME. Matrix metalloproteinases (MMPs) secreted by cancer and stromal cells [37] can promote tumor vascularization, as demonstrated with MMP-9 in pancreatic tumors [47] and glioblastomas [48], and MMP-2 in chondrosarcomas [49], through the release of angiogenic factors including Vascular Endothelial Growth Factor (VEGF) [47,48]. Interestingly, highly differentiated cancer cells could also form *de novo* microvascular channels themselves, a phenomenon referred to as vasculogenic mimicry [50–53]. Conversely, hypoxia [54] and acidosis [55] induced by a defective vascularization cause alterations, *e.g.*, epigenetic changes, in cancer cells, thereby increasing their invasiveness and aggressiveness.

The extracellular matrix is another important component of this environment. NCA effects can promote the reorganization of the extracellular matrix, to promote proliferation and invasion, *e.g.*, tumor cells can recruit and activate fibroblasts that synthesize and secrete serine proteases and MMPs. In turn, these proteases degrade and remodel the extracellular matrix [40] in order to promote tumor progression [56]. Cancer-associated fibroblasts also increase extracellular matrix production [57]. In turn, the matrix deposition reduces the ability of chemotherapeutic drugs to penetrate a tumor [58], and reduces the amount of oxygen and nutrients reaching the center of the tumor [44, 57].

## 3. CA and NCA effects in cancer cell ecology

A mutation may not impact similarly all the subclones within a given tumor. NCA effects of mutations could modulate the fitness of locally coexisting subclones. Therefore, we should focus on potential effects of mutations on every subclone, in order to determine their impact on the entire tumor.

### 3.1. CA and NCA effects on cancer cell fitness

#### 3.1.1. Trade-offs (cost–benefit balance) of CA and NCA effects

The carriers of mutations are the only cancer cells to incur their CA effects on fitness. For instance, in an acidic environment, carriers of mutations conferring a resistance to acidosis are the only cells found to survive [59]: these cells absorb the cost of producing resistance, but also benefit from surviving acidosis. In contrast, while carriers of mutations may incur changes in fitness due to intracellular changes, the fitness of other cancer cells can be impacted by NCA effects of these mutations, involving direct interactions or changes in the ME. For example, for an entire tumor to be acidic, only a subset of cells are needed to produce acidic metabolites that diffuse in the ME. The carriers of this trait therefore bear the costs and benefits of down regulating their respiratory pathways, whereas the costs and benefits of living in an acidic environment are shared by every cancer cells living in it [59]. In this particular example, shared costs and benefits of ME acidosis include not only the high toxicity for all the cells in the tumor, but also the degradation of the ECM [60], probably by up-regulating the expression of MMPs [61, 62].

Since NCA effects can remotely change the fitness of other cells, it raises questions about cell sensitivity, *i.e.*, which cells are affected by NCA effects. NCA effects can affect every adjacent cancer cell, being only limited by diffusion laws, notably when these traits induce metabolic [49,59,60] or structural changes [57,58]. They can also depend on the specific cell subtypes, *e.g.*, through the secretion of a cytokine that support the proliferation of a specific population of surrounding cells that expressed the appropriate receptor for that cytokine. [63].

Thus, NCA effects can also confer a cost to stromal cells in certain situations: (i) normal cells can suffer from factors which do not precisely target cancer cells (*e.g.* acidic microenvironment [60,64]); (ii) stromal cells recruited by cancer cells can bear the production cost of some NCA effects [39,40]; and (iii) due to differences in genetic expression, normal cells could suffer from factors which favor some malignant subclones (which is actually the case for every trait driving tumor progression, at the expense of the host organism).

#### 3.1.2. NCA effects and niche construction

The effect of all mutations on fitness is entirely context-dependent (dependent on both the genetic context and the environmental context) [65]. Although special attention was placed on the genome landscape in which new mutations emerge to evaluate their impact [7,66], their effects on the ME create a diversity of ecological niches that in turn modulate the fitness of the subclones [16,67].

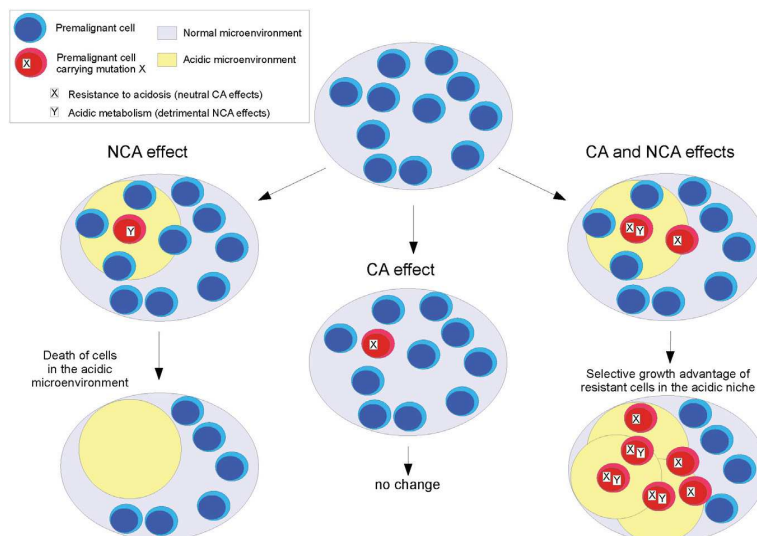
For example, let us consider a mutation X conferring resistance to acidosis and a mutation Y conferring a high glycolytic metabolism [49, 59,60,64]. Mutation X alone is neutral or deleterious for its carriers (see Fig. 1, CA effect), whereas mutation Y alone induces the release of toxic acidic metabolites in the ME (see Fig. 1, NCA effect). When carriers of mutation Y and those of mutation X share the same local microenvironment, mutation X becomes driver as it confers a growth advantage to its carriers in the acidic ME generated by mutation Y (see Fig. 1, CA and NCA effects) [60,68]. Carriers of mutation X will grow as long as mutation Y is present in the microenvironment. Furthermore, not only do mutations have context-dependent effects due to the impact that cancer cells themselves have on their environment, but major drivers of carcinogenesis (*e.g.*, aging, smoking, etc.) also take part in constructing the tumorigenic niche, leading to altered selection for oncogenic mutations [69–71].

### 3.2. CA and NCA effects and biological interactions

By considering tumors as communities of cancer cells proliferating in the same stroma [9,13], the biological interactions involving CA and NCA effects should be better investigated (see Table 1).

#### 3.2.1. Competition

Given that resources are limited in the ecological niche of cancer cells and potentially every cancer cell competes with each other within the tumor, competition is the most important biological interaction between cancer cells [9,13]. CA effects determine the growth and uptake rates of cancer cells for oxygen, substrate and growth factors. They determine their carriers' performance to exploitative competition, by simple consumption [18,72]. NCA effects are involved in interference competition by directly impeding the growth and survival of other subclones, *e.g.*, cancer cells inhibit each other's growth by diffusion of



**Fig. 1.** Niche construction with CA and NCA effects. Mutation X confers a resistance to acidosis to its carriers: it has CA effects and confers a neutral phenotype to its carriers. Mutation Y confers an acidic metabolism to its carriers, and elicits microenvironmental acidosis: it has NCA effects and confers a detrimental phenotype to every cell in the local ME. When they appear together in the same ME, mutations X and Y establish a population of resistant cancer cells in an acidic niche.

**Table 1**  
Biological interactions categorized by effects.

Effect on self	Effect on partner	Interaction
Beneficial	Beneficial	Mutualism
	Neutral	Commensalism
	Detrimental	Antagonism
Neutral	Beneficial	Amensalism
	Neutral	Neutralism
	Detrimental	Amensalism
Detrimental	Detrimental	Competition

soluble factors [73–76] and the high glycolytic metabolism of cancer cells is a strategy to outcompete the subclones not carrying resistance-conferring mutations [49,59,60].

### 3.2.2. Mutualism

As cancer cells commit to competition both with each other and with normal cells, the emergence of collective organization appears as a paradox [43,77]. Yet, many theoretical [78–82] and empirical studies [18,29,56,63,83–87] have provided evidence that cooperative (mutualism and commensalism) relationships occur between cancer cells. NCA effects can involve the production of enough diffusible factors to supply other cells' needs, either directly [56,63,84,85,87], or through the recruitment of stromal cells that re-shape the ME [10,37,88,89].

Cooperation between cancer cells can occur through several mechanisms. A beneficial mutation can promote the growth of the tumor cells and the surrounding cells if the produced goods are diffusible enough and become public goods [80,82,87]. Cooperation between cancer cells could take an altruistic turn when NCA effects are costly for their producers and beneficial to other subclones [78], generating a compensatory relationship through indirect fitness benefits (e.g.,

relatedness) and enforcement of direct fitness benefits (e.g., reciprocity, see Fig. 2.a). Yet, kin selection is presumably unlikely to evolve under the timeframe of tumorigenesis [90], but reciprocal altruism could occur for cancer cells involved in symmetric interactions.

### 3.2.3. Antagonism

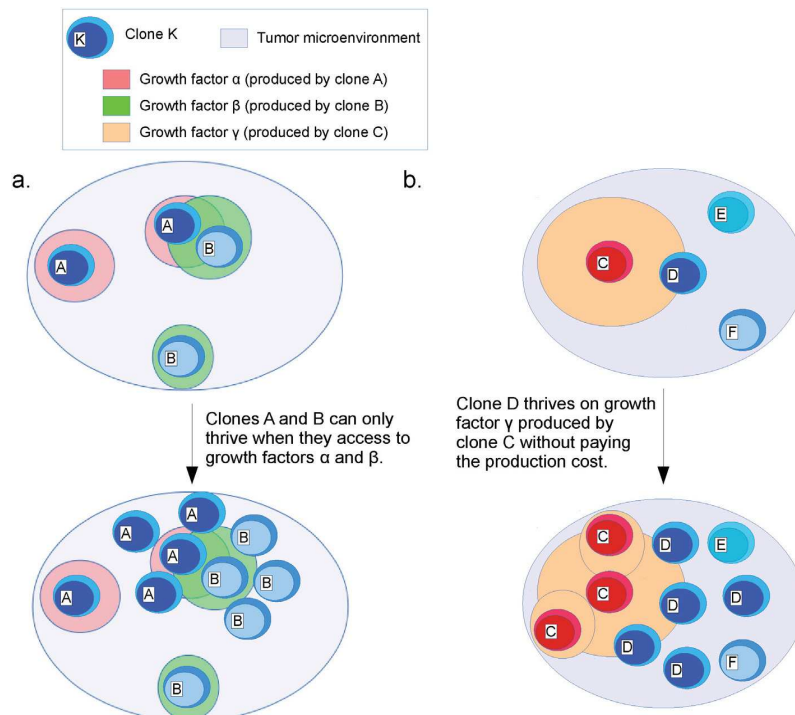
Antagonism is a relationship in which one species (e.g., predator or parasite) exert negative effects on another (e.g., prey or host), and gain some growth and reproductive benefit in return. A parallel with NCA effects involving the recruitment of stromal cells by malignant cells in neoplasms can be easily established. Such relationships could also be considered between cancer cells, since mutualism is at equilibrium with exploitation in many cases [91–93]. Some subclones could easily hitchhike others' metabolic investments [13,82,87], since NCA effects often involve free diffusible factors (see Fig. 2.b).

## 3.3. CA and NCA effects in tumor progression

### 3.3.1. CA and NCA effects shape tumor heterogeneity

CA effects confer uneven costs and benefits: e.g., in the presence of a growth factor, the subclones with an increased expression of their membrane receptors gain increased proliferative capacities [16,94], and therefore outcompete the cells that have a lower expression of this trait. Thereby, there is theoretical evidence that CA effects may not support genetic and epigenetic heterogeneity [15,66,95,96]: mutations that only harm their carriers hardly emerge, whereas mutations that only benefit their carriers likely result in clonal expansions to the expense of noncarrier clones.

On the contrary, NCA effects can impact the absolute fitness values of cancer cells belonging to diverse subclones without systematically inducing a competitive exclusion [59,60]. The effects of a diffusible factor



**Fig. 2.** Mutualism and exploitation between cancer cells. Clones A, B and C respectively release growth factors in their local microenvironment. a. Clones A and B both benefit from growth factors produced by each other: they are therefore in a mutualistic relationship. b. Clone D exploits growth factors produced by clone C without paying their production cost: they are therefore in an antagonistic relationship.

released in the ME depend on each subclone's sensitivity to this factor [63,81,84,85,97], but diverse subclones can be maintained by this stimulation. The simple production of a diffusible factor that is potentially beneficial to every cancer cell can support their growth [18,29,56] and therefore stabilize the coexistence of both producers and non-producers [82,87,98]. In a further extent, a multitude of local niches can emerge due to the limited diffusion of NCA effects. Therefore, within the same tumor, this diversity of local niches is not only able to select a multitude of dominant subclones, but also able to generate nonheritable diversity due to phenotypic plasticity of cancer cells [9, 99,100]. Thereby, among substantial sources of intratumor diversity [9,10], NCA effects have the significant interest of easily explaining ecological dynamics of phenotypic diversity.

### 3.3.2. CA and NCA effects shape cancer progression

The load of NCA and CA effects in a tumor has also substantial consequences on cancer progression. Notably, the co-occurrence of mutations can result in clonal interference [2,101,102], *i.e.*, to an intense selection on their CA effects. That is, selective pressures, whether originating from clonal interactions or from ME constraints, tend to intensify clonal competition and thus to drive the evolution of tumors towards aggressiveness and invasiveness [6,103]. Conversely, NCA effects can both donate supportive conditions and establish a spatial heterogeneity in the ME and therefore decrease clonal interference [104,105], which slows down the emergence of aggressive subclones [101]. Besides, by favoring or being neutral towards tumor heterogeneity, NCA effects result in bet-hedging: that is, they maintain a pool of neutral traits which might confer competitive advantages in case of ME change, *e.g.*, drug resistance [9,44,106]. NCA and CA effects are thus the complementary keys for cancer progression, and their necessary coexistence may explain that most of solid tumors are highly heterogeneous.

## 4. Perspectives

### 4.1. Tumors as ecosystem paradigms

Cancer cells in a given tumor form a community of subclones in interaction with each other and with their ME, therefore they can be considered as an ecosystem [13,107–110]. Given the diversity of subclones and traits that coexist in the tumor, it would make sense to design a network of biological interactions between coexisting clones, *i.e.*, a clonal network [111,112]. All the subclones being linked to each other to some degree in the local ME, any external perturbation in the network is likely to affect all the subclones. Notably, ecosystems are sensitive to the population dynamics of keystone species, and likewise “keystone subclones” could be identified and targeted thanks to CA and NCA effects. Several authors suggested therapeutic strategies that would drive tumors to clonal meltdown by controlling the balance between detrimental and beneficial mutations [5,113,114]. Such strategies could be valuable at the tumor ecosystem level, since CA and NCA effects underlie the interactions between subclones and with their ME. Notably, theoretical [72,115] and experimental studies [18] raised the idea that a very competitive subclone could outcompete the others in a tumor. By disrupting NCA effects involved in the social network of tumors, we could decrease the support of the ME to cancer cells, thus leading to the extinction of some of the subclones [116,117], and decrease tumor heterogeneity [118] with two major consequences: (i) a homogeneous population of cancer cells is much easier to target; (ii) the outcompeting of “keystone subclones” could cause the collapse of the entire tumor.

However, such an approach could also select the most aggressive subclones in tumors, as observed following classic chemotherapeutic approaches. Both the strong selective pressure applied to the remaining subclones and the competitive release could make the residual tumor more aggressive [2]. Besides, the intensification of competition within the host could quickly promote the destruction of the organ and even

the selection of dispersive, metastatic phenotypes [72,119]. Thus, an efficient therapy should confirm the vulnerability of the most aggressive clones prior to promoting the competition [18,115].

### 4.2. Targeting the public goods and their producers

A basic strategy to disrupt NCA effects in tumors consists in therapeutically targeting their producers, *i.e.*, the carriers of the given mutations. The reduction of the producer population should slow down tumor progression, potentially beyond a threshold under which producers are not sufficient to maintain the tumor population [18, 120]. However, producers of NCA effects are as likely as other subclones to carry drug resistance; besides several subclones are likely to carry the same independently acquired mutation (equivalence principle [16]) and all of them should be targeted to eliminate the trait. Thus, a more general and reliable strategy consists of directly targeting the public goods involved in NCA effects [82,87,121,122], by either targeting the caused ME changes [84] or by making it difficult for cancer cells to access the modified ME. This strategy also seems to bring new insights to overcome the problem of drug resistance [121]. Additionally, recruited stromal cells could also be interesting targets: although they actively take part in tumor progression, they rarely mutate and are thus less likely to carry drug resistance.

### 4.3. Disrupting the spatial structure of the tumor ecosystem

As a spatially-structured environment, the tumor ecosystem promotes clonal diversity, partly through mechanisms of niche segregation. The spatial structure of microbial communities is known to impede interference between co-competitors [123,124], while uneven distribution of resources supports the coexistence of subpopulations segregated around peaks of local resource abundance [105,107,108]. Niche segregation results in limited competition in tumors [101,104], therefore well-mixed populations of cancer cells would have better chances to reach competitive exclusion [18,72]. By shifting the diffusivity of NCA effects, changes in the ME spatial structure would result in alterations in the tumor clonal network, and notably homogenize the selective pressures driven by NCA effects in the entire tumor. Though, we should be aware that a better diffusivity has some drawbacks on subclonal diversity: especially, a better access to diffusible factors may support the coexistence of both producer and nonproducer subclones [82,87].

### 4.4. Towards further investigation of CA and NCA effects in tumors

A precise description and quantification of tumor ecosystems is needed in order to fully understand the role of CA and NCA effects in cancer, by keeping in mind that the gene–phenotype relationship is probably not straightforward for CA and NCA effects driving carcinogenesis. The frequencies of mutations across tumors [125] and across cells [126] are assumed to inform about their fate in clonal evolution: the most prevalent mutations are the most transmitted and therefore, should presumably be the most beneficial. Though, not only was this approach shown to inefficiently identify genes carrying driver mutations [127], but it also is unable to identify mutations associated with NCA effects, as they can drive tumor growth without necessarily increasing in frequency [18,83]. Thus, it is crucial to also investigate the functional consequences of mutations (*i.e.*, phenotypic traits) and their evolution over cell divisions, to really assess the respective impacts of all the sampled mutations.

Functional studies would also have the advantage of helping to characterize the social network in tumors, and notably the quantification of interactions within and between subclones [63,112,128]. Interestingly, many relevant comparisons have been made between tumors and microbial communities [44,46], notably on their structures, diversity and rates of evolution. Importantly, although NCA effects have also been proposed to have crucial implications in microbial communities

[44,129,130], their roles in oncogenesis have been so far underappreciated. As parallels with these ecosystems may thus help to better delineate CA and NCA effects driving tumor structure, this consolidate the evidence that cancer biology should not be addressed without ecological or evolutionary perspectives any longer.

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## Glossary

**Ecosystem:** A community of living organisms in conjunction with the nonliving components of their environment, interacting as a system.

**Keystone species:** A species that has a disproportionately large effect on its environment relative to its abundance.

**Driver mutation:** A mutation that directly or indirectly confers a selective growth advantage to the cell in which it occurs.

**Passenger mutation:** A mutation that confers either no selective growth advantage or a selective growth disadvantage to the cell in which it occurs.

**Cell-autonomous effect:** The effect of a gene which confers the corresponding phenotype to the cells that express it.

**Non-cell-autonomous effect:** The effect of a gene which confers the corresponding phenotype to cells that do not express it.

**Stroma:** The supporting framework of an organ, usually composed of connective tissue cells.

**Paracrine signaling:** A form of cell signaling in which the target cell is near the signal-releasing cell.

**Autocrine signaling:** A form of cell signaling in which a cell secretes an agent that binds to autocrine receptors on the same cell, leading to changes in the cell.

**Equivalence principle:** The fact that multiple different (epi)mutations can produce similar phenotypes, so that they can be similarly selected by the tumor microenvironment.

**Clone:** A group of cancer cells that are derived from the same cell.

**Subclone:** A population of genetically identical cancer cells, descending from the same clone.

**Carrier:** A cancer cell that has inherited a particular allele or mutation.



## 6 Ecologie tumorale et diversité clonale

**Titre :** *Non-cell-autonomous effects yield lower clonal diversity in expanding tumors.*

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1 **Non-cell-autonomous effects yield lower clonal diversity in expanding tumors.**

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9 **keywords:** intratumor heterogeneity; cancer; ecology; evolution; interactions; driver/passenger  
10 mutations

11

12 **Abstract**

13 Recent cancer research has investigated the possibility that non-cell-autonomous (NCA) driving  
14 tumor growth can support clonal diversity (CD). Indeed, mutations can affect the phenotypes not  
15 only of their carriers (“cell-autonomous”, CA effects), but also sometimes of other cells (NCA  
16 effects). However, models that have investigated this phenomenon have only considered a restricted  
17 number of clones. Here, we designed an individual-based model of tumor evolution, where clones  
18 grow and mutate to yield new clones, among which a given frequency have NCA effects on other  
19 clones' growth. Unlike previously observed for smaller assemblages, most of our simulations yield  
20 lower CD with high frequency of mutations with NCA effects. Owing to NCA effects increasing  
21 competition in the tumor, clones being already dominant are more likely to stay dominant, and  
22 emergent clones not to thrive. These results may help personalized medicine to predict intratumor  
23 heterogeneity across different cancer types for which frequency of NCA effects could be quantified.

24

25 **1. Introduction**

26 Patient biopsies reveal that most of solid tumors display a high diversity of cancer cell  
27 subtypes.<sup>1</sup> This intratumor heterogeneity (ITH) early emerges during carcinogenesis<sup>2</sup> and is  
28 correlated with cancer progression.<sup>3</sup> It predicts both cancer aggressiveness<sup>2,4,5</sup> and post-therapeutic  
29 recurrence risk.<sup>6,7</sup> Two main mechanisms have emerged to explain the coexistence of numerous  
30 phenotypes within the same tumor.<sup>8,9</sup> On the one hand, cell phenotypic plasticity, especially the  
31 existence of cancer stem cells, allows cells with a same genotype (i.e. a clone) to display different  
32 phenotypes, due to epigenetic differences or differences in cell signaling pathways.<sup>10,11</sup> On the other  
33 hand, clonal evolution generates a range of genotypes across time, due to the accumulation of  
34 mutations in cancer cells' genomes.<sup>12</sup>

35 Clonal diversity (CD) is the genetic component of phenotypic diversity displayed by tumors. It is  
36 yielded by the branching clonal evolution in progress in every tumor: i.e., the accumulation of  
37 mutations yields a range of clones that coexist in similar frequencies within the same micro-  
38 environment (ME).<sup>13-15</sup> A part of these mutations can impact growth rates, and eventually the  
39 evolution of frequencies across time.<sup>16,17</sup> Among them, beneficial mutations (known as *drivers*)  
40 usually speed up the growth kinetics of the carrier clones,<sup>18</sup> which may eventually lower CD.<sup>19</sup> If  
41 drivers are not rare in tumors and should negatively impact CD, some of them can nevertheless  
42 promote their carriers' growth without increasing in frequency.<sup>20,21</sup> Indeed, if mutations can impact  
43 their carriers' growth through cell-autonomous effects (CA effects), they can also impact other  
44 noncarrier clones' growth, through non-cell-autonomous effects (NCA effects<sup>22,23</sup>).

45 The significance of NCA effects for CD is increasingly addressed in cancer research.<sup>23-25</sup> NCA  
46 effects of mutations were found to directly impact the growth of noncarrier clones by many  
47 different mechanisms (Supporting information, Table S1).<sup>23</sup> This body of NCA effects is already  
48 taken into account in the design of patient-derived models of tumors to yield similar ITH *in vitro* as  
49 *in vivo*,<sup>22</sup> but *in silico* models of CD evolution have very poorly addressed the impacts of NCA  
50 effects so far. Most of models studying ITH implicitly exclude NCA effects,<sup>17,19,26,27</sup> while models

51 involving NCA effects in tumor evolution do not measure the impacts on ITH.<sup>28,29</sup> Though, in a  
52 data-fitted model, Marusyk et al. predicted a higher CD on the long run when a single clone could  
53 non-cell-autonomously promote the exponential growth of a limited number of other clones.<sup>21</sup> But  
54 how numerous different NCA effects impact CD on the long run in the tumor remains unclear.

55 In the absence of NCA effects, only neutral and beneficial mutations persist. The latter accelerate  
56 the emergence of new clones through divisions, which consequently supports CD on the long run.  
57 However, when clones carry mutations with NCA effects, they could also shape the growth kinetics  
58 of noncarrier clones. On the one hand, mutations with NCA effects could balance the growth  
59 kinetics of the diversity of preexisting clones in the tumor: beneficial mutations with NCA effects  
60 could allow slow growing clones (potentially carrying detrimental mutations) to persist, and  
61 detrimental mutations with NCA effects could mitigate the outgrowth of fast growing clones. This  
62 would allow the coexistence of clones at similar frequencies, and thus support CD. On the other  
63 hand, mutations with NCA effects could exaggerate the differences in growth kinetics already  
64 existing between clones: detrimental mutations with NCA effects could also limit the probability for  
65 emerging clones to reach high frequencies, and beneficial mutations with NCA effects could  
66 accelerate the growth kinetics of already fast growing clones. Without necessarily limiting clonal  
67 richness, this would exacerbate the differences between clonal frequencies and limit equitability,  
68 thus reducing CD.<sup>30</sup> The possible outcomes of CD when tumor growth is driven by NCA effects, are  
69 therefore challenging to forecast.

70 In order to test the impact of NCA effects on CD evolution, we follow the branching of clones  
71 interacting with each other through the NCA effects of their mutations. Since mathematical models  
72 of cell growth have tractability issues at simultaneously considering large numbers of clones, we  
73 choose the framework of individual-based models.<sup>31</sup> In our model, cells divide and die according to  
74 division and death rates determined by CA and NCA effects. Across divisions, cells can mutate and  
75 therefore produce new clones. In order to stay apart from spatial issues, we assume that the  
76 diffusion of NCA effects is instantaneous from one cell to another and does not depend on the

77 density of cells in the tumor. This model allows quantifying CD (assumed to be represented by  
 78 Simpson index) across time and divisions, depending on the frequency of mutations with NCA  
 79 effects. Thus, in order to disentangle the link between NCA-driven growth kinetics and CD, we  
 80 simulated tumors growing either during a fixed number of generations, or until they reached a fixed  
 81 size, whereas CA and NCA effects had various impacts on clonal growth kinetics.

82

## 83 **2. Methods**

84 The goal of our individual-based model is to implement the stochastic evolution of interacting,  
 85 clonally-reproducing cells, allowing us to monitor CD for a range of conditions in mutations, tumor  
 86 age and tumor size. The model is described in Text S1 and Figure 1, and the main algorithm is  
 87 detailed in Text S2.

88

### 89 **2.1 Model behavior**

90 We start each simulation with a self-replicating population of  $N_0$  noncancerous cells. These cells  
 91 divided and died at the exact same basal rate  $b_0 = d_0$ , and thus their population size only  
 92 experienced stochastic fluctuations, corresponding to physiological conditions of self-renewing  
 93 stem cells in tissues. Across divisions, each cell had a probability  $\mu$  to mutate and to produce a new  
 94 clone, which we considered to be cancerous (see Fig. 1A). At each timestep, probabilities of  
 95 division and death events were computed for each cell, before to be eventually applied, so that these  
 96 events could be implemented in any order without influencing their respective outcomes:

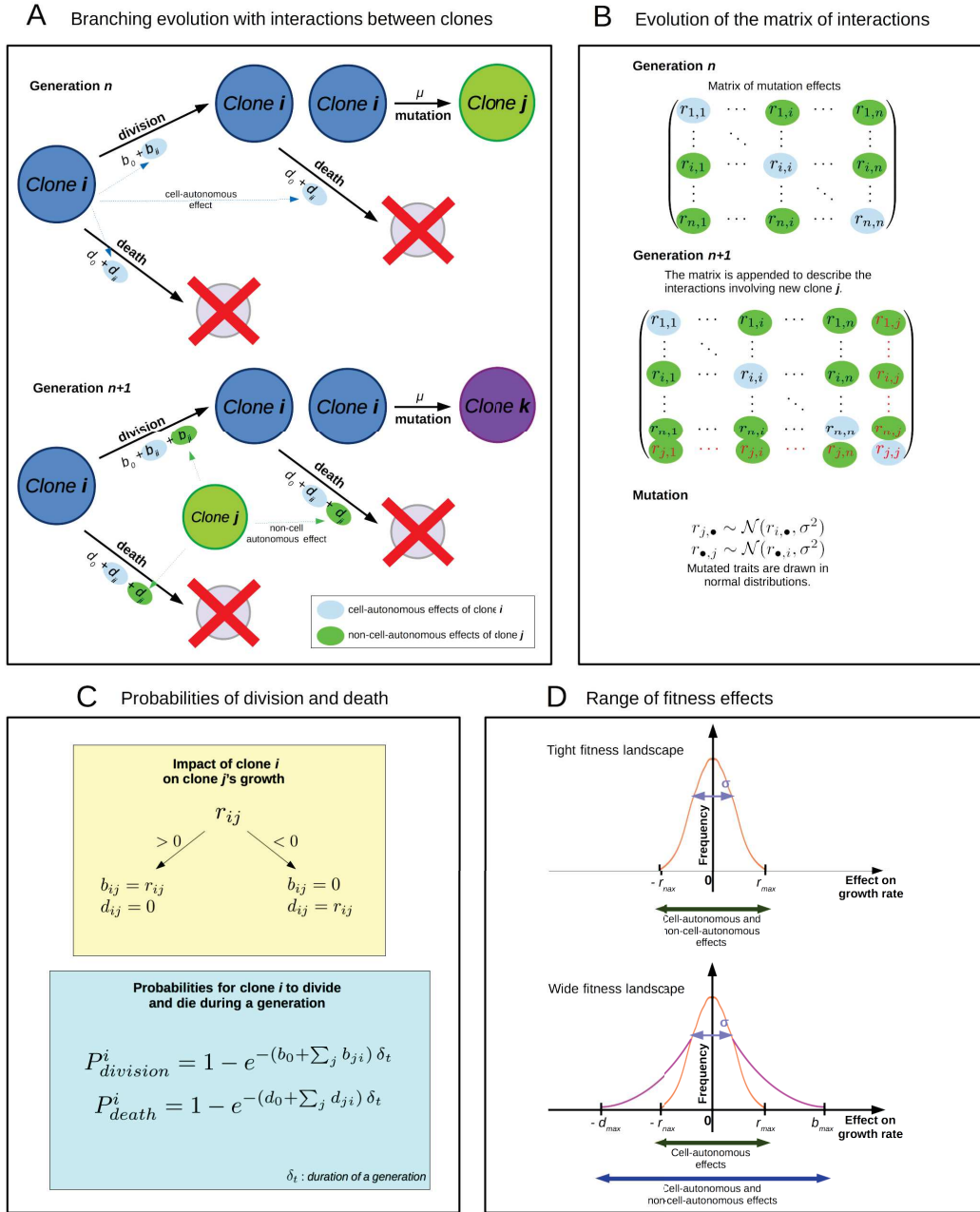
$$97 \quad P_{division}^i = 1 - \exp(-(b_0 + \sum_j b_{ji}) \delta_t)$$

$$98 \quad P_{death}^i = 1 - \exp(-(d_0 + \sum_j d_{ji}) \delta_t)$$

98 for  $i$  being the identity of the clone. According to these equations, every new clone grew  
 99 exponentially according to basal division and death rates, but mutations could also confer them  
 100 growth advantages or losses that subsequently raised or lowered their population sizes. These  
 101 mutation effects on division and death rates were drawn in a fitness landscape, and could be either  
 102 CA (only affecting the clone carrying the mutation,  $r_{ii}$  for an impact of clone  $i$  on its own division

103 and death rates) or NCA (possibly affecting other clones,  $r_{ij}$  for an impact of clone  $i$  on clone  $j$ 's  
104 division and death rates, see Fig. 1B–C). The values of mutation effects could be either positive or  
105 negative, and were add up to basal division and death rates according to their sign: positive  
106 mutations were add up to division rates, *i.e.*,  $b_{ji} = r_{ji}$  if  $r_{ji} \geq 0$ ; and negative ones to death rates,  
107 *i.e.*,  $d_{ji} = r_{ji}$  if  $r_{ji} < 0$ . CA and NCA effects were considered as frequency- and density-  
108 independent, *i.e.*, any clone could non-cell-autonomously impact others, provided it was composed  
109 of at least one cell. The values of mutation effects could be either positive or negative: effective  
110 division rates were then computed by adding all the positive mutation effects to the basal division  
111 rate, and effective death rates by adding all the negative mutation effects to the basal death rate. In  
112 order to keep an exponential growth of cancer cells,<sup>32</sup> division and death rates could not exceed  
113 maximal rates  $b_{max} = d_{max}$ , and mutation effects could not produce fitness variations higher than  
114  $r_{max}$  (Supporting information, Tab. S2 for values). Besides, cancerous cells were as likely as  
115 noncancerous cells to mutate and to produce new clones.

116 Most mutations do not produce large fitness variations during cancer,<sup>33</sup> even though most cancers  
117 have their genomes highly instable.<sup>34,35</sup> Mutated traits were thus drawn in normal distributions  
118 centered on the resident traits, with standard deviation  $\sigma$  (see Fig. 1B). This ensured that new  
119 mutants were phenotypically close from the clones that they derived from, in order to let mutations  
120 accumulate in clones. Among mutation events, we enforced different frequencies of mutations with  
121 NCA effects, ranging from 0 to 50% of mutations. Besides, in order to distinguish the impacts of  
122 NCA effects on growth kinetics from those of CA effects, we performed simulations for two distinct  
123 fitness landscapes (see Fig. 1D). In the condition referred to as *tight fitness landscape*, the maxima  
124 of division and death rates were fixed to  $r_{max}$ . In the condition referred to as *wide fitness*  
125 *landscape*, the maxima of division and death rates were fixed to  $b_{max} = d_{max}$ .



126

127 **Figure 1: Individual-based model of clonal evolution with interactions.** (A) Model architecture:  
 128 division and death rates depend both on basal rates ( $b_0$  and  $d_0$ ) and on the effects of mutations on phenotype. Mutations  
 129 affect clonal growth kinetics through a matrix of interactions, where  $b_{ji}$  and  $d_{ji}$  are the effects of clone  $j$  on clone  $i$ 's  
 130 growth. (B) Evolution of the matrix of interactions: the matrix of interactions encompasses both cell-autonomous  
 131 effects ( $b_{ii}$  and  $d_{ii}$ ) and non-cell-autonomous effects ( $b_{\bullet,i}$  and  $d_{\bullet,i}$ ). When new clones arise by mutation, the matrix is

132 appended with new interaction coefficients  $r_{\bullet,\bullet}$  which are drawn in normal distributions centered on interaction  
133 coefficients of the resident clone. (C) Probabilities of division and death: interactions coefficients are distinguished on  
134 whether they benefit or harm the recipient clone. They are then added to basal division and death rates to produce  
135 effective division and death rates. These effective rates are then used as parameters for exponential distribution in which  
136 division and death events are drawn. (D) Range of fitness effects: in a tight fitness landscape, the maxima of division  
137 and death rates are set to the range of mutation effects distribution, *i.e.*, cell-autonomous and non-cell-autonomous  
138 effects similarly impact the division and death rates. In a wide fitness landscape, the maxima of division and death rates  
139 are higher than the maxima of mutation effects distribution, *i.e.*, non-cell-autonomous effects can have distinct impacts  
140 on clonal growth rates from cell-autonomous effects<sup>7</sup>.

141

142

143 We considered that the whole cell population formed a tumor as soon as the whole cell population  
144 (as a sum of all clone sizes) has grown enough to consider that cancerous clones outgrow enough to  
145 be driven to cancer progression (tumor formation is assumed to have been reached at  $N = \alpha_t N_0$ ).  
146 We then recorded the emergence of new clones and the size of every clone at each generation. In  
147 order to determine the impact of NCA effects on CD, simulations could stop when they reached a  
148 final condition of fixed time or fixed size: (i) either when tumor evolution had been recorded during  
149 a given number of generations  $t_{max} = 300$  generations; (ii) or when tumor had exceeded a given  
150 size  $N_{max} = 3 * 10^5$  cells. These two conditions allowed to track the evolution of CD during the  
151 very first steps of cancer progression, when diversity emerges.<sup>36</sup>

152 This framework is based on parameters which have rarely been addressed in empirical studies, and  
153 mostly in theoretical studies. We thus performed simulations on parameter values used in similar  
154 models (Supporting information, Tab. S2). Even though these values were not all biologically  
155 motivated, they allowed us to compare our results with other studies addressing NCA effects and  
156 CD. Thus, in order to test the sensitivity of CD and growth kinetics to other parameters, the  
157 parameter space was explored through a method of Latin Hypercube Sampling (LHS<sup>37</sup>) as  
158 implemented in function randomLHS of the statistical software R.<sup>38</sup> LHS was performed on uniform  
159 distributions (rather than normal distributions, in order to alleviate the uncertainty on parameter



160 values) bounded in 20% variations of the values displayed in Table S2 (see “80% Value” and  
161 “120% Value”). In order to avoid outliers among simulations, we did not record simulations for  
162 which tumor size did not reach  $\alpha_t N_0$  cells within 10000 generations, or  $N_0$  cells within 1500  
163 generations after tumor formation, nor those which dropped below  $N_0$  cells (from 1 to 10% of  
164 simulations, depending of the condition tested).

165

## 166 **2.2 Data analysis**

167 For each condition, we performed 500 simulations reaching the expected final status. At the end of  
168 each simulation, we quantified clonal diversity with Simpson index. This measure, which was  
169 previously used in other models addressing of tumor heterogeneity,<sup>19,26</sup> accounts for both clonal  
170 richness and equitability, while being bounded. For  $p_i$  being the frequency of clone  $i$  in the tumor,  
171 Simpson index was computed as:

$$172 \quad H = 1 - \sum_i p_i^2$$

173 We obtained similar patterns when measuring clonal diversity with Shannon index (Supporting  
174 information, Fig. S1).

175 We also recorded the number of generations (tumor age) necessary to reach  $N_{max}$  cells and the  
176 tumor size after  $t_{max}$  simulations for simulations during a given time. In order to have a common  
177 measure of growth kinetics for both types of simulations, mean tumor growth rate was then  
178 computed for each simulation as:

$$179 \quad \text{Tumor growth rate} = \frac{\text{Tumor size}}{\text{Tumor age}}$$

180 These measures were not normally distributed (assessed by a Shapiro-Wilk test), and did not follow  
181 homoscedasticity (assessed by a Brown-Forsythe test). Instead of an ANOVA, we thus performed  
182 linear regressions on both Simpson indexes and tumor growth rate as functions of the frequency of  
183 mutations with NCA effects. We kept models with maximal  $R^2$ .

184 In order to discriminate the impacts of NCA effects relatively to other parameters, we performed a

185 sensitivity analysis for Simpson index and tumor growth rate. We screened for both linear and  
186 nonlinear relationships with these measures, so that rank-transformation of the data was necessary.  
187 We thus computed partial rank correlation coefficients (PRCC<sup>37</sup>) depending on minimal tumor size  
188  $\alpha_t N_0$ , the basal division rate  $b_0$ , the variance of mutation effects  $\sigma$ , the range of mutation effects  
189 distribution  $r_{max}/b_0$ , the mutation rate  $\mu$ , and the frequency of mutations with NCA effects. PRCC  
190 were computed using a variant of function pcc (modified to deliver p-values) of the statistical  
191 software R (package sensitivity<sup>39</sup>).

192 To assess the effect of growth kinetics on CD regardless of NCA effects, we computed PRCC of  
193 Simpson index depending on minimal tumor size  $\alpha_t N_0$ , the basal division rate  $b_0$ , the variance of  
194 mutation effects  $\sigma$ , the range of mutation effects distribution  $b_{var}/b_0$ , the mutation rate  $\mu$ , and tumor  
195 growth rate. PRCC residuals of Simpson index and tumor growth rate were extracted to investigate  
196 for potential correlations with Pearson correlation coefficient.

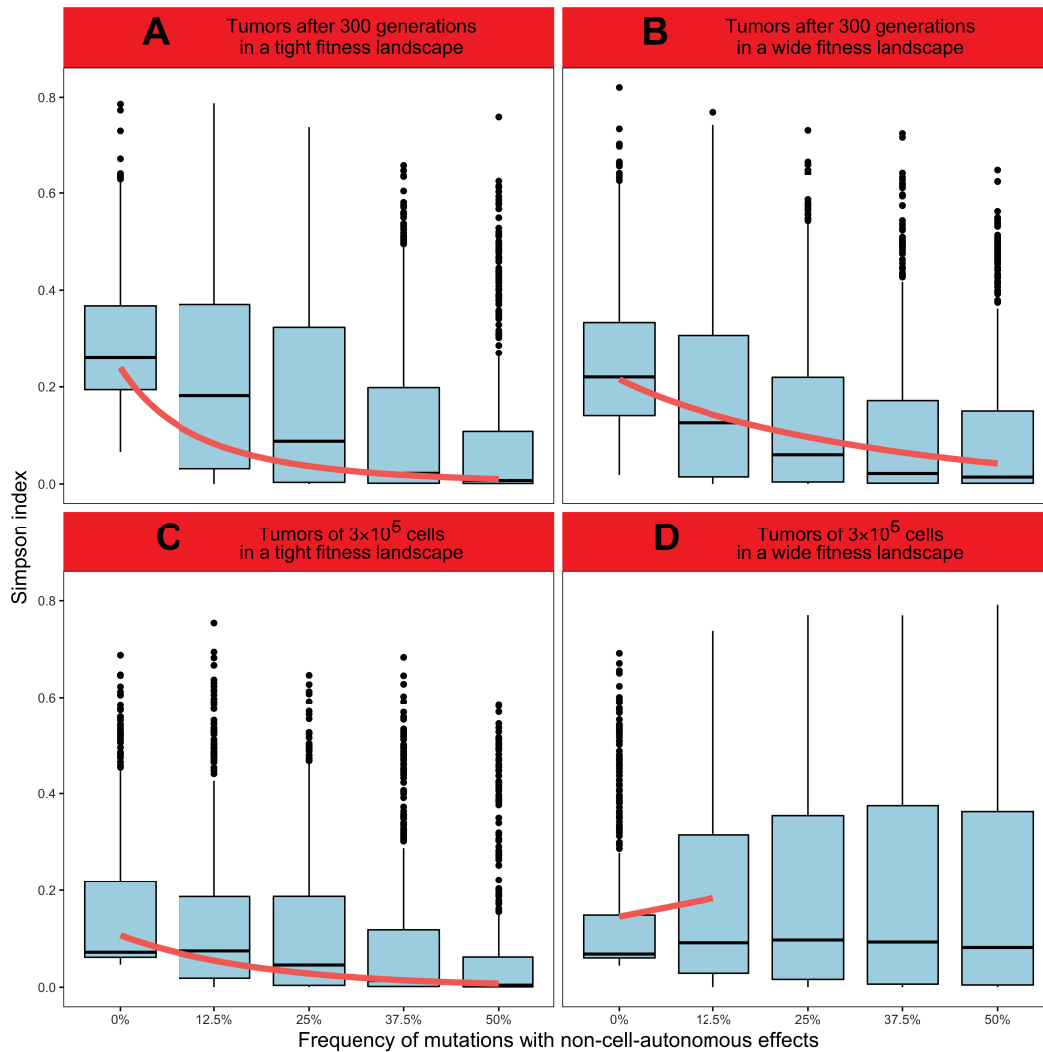
197

### 198 **3. Results**

#### 199 **3.1 Impacts of NCA effects on clonal diversity**

200 We simulated 2500 tumors during 300 cell generations, in both a tight and a wide fitness landscape.  
201 In a tight fitness landscape, Simpson index decreases when the frequency of mutations with NCA  
202 effects increases (Fig. 2A, linear regression:  $\log[\text{Simpson index}] = -4.49 \pm 0.17 \sqrt{f_{NCA}}$ ,  $t = -25.62$ ,  
203  $p < 2.2 \cdot 10^{-16}$ ,  $R^2 = 0.208$ ). The sensitivity analysis supports this negative significant association with  
204 the frequency of mutations with NCA effects (PRCC,  $r = -0.431$ ,  $p < 2.2 \cdot 10^{-16}$ ), as well as with the  
205 range of mutation effects (ranging from  $1.6 b_0 = 1.6 d_0$  to  $2.4 b_0 = 2.4 d_0$ ,  $r = -0.059$ ,  $p = 3.4 \cdot 10^{-3}$ ) and  
206 with minimal tumor size (ranging from  $2.4 N_0$  to  $3.6 N_0$ ,  $r = -0.051$ ,  $p = 1.1 \cdot 10^{-2}$ , Supporting  
207 information, Tab. S3). For tumors simulated in a wide fitness landscape, we observed the same  
208 relationship: Simpson index is negatively associated with the frequency of mutations with NCA  
209 effects (Fig. 2B, linear regression:  $\sqrt{\text{Simpson index}} = -0.38 \pm 0.02 \sqrt{f_{NCA}}$ ,  $t = -20.78$ ,  $p < 2.2 \cdot 10^{-16}$ ,  
210  $R^2 = 0.147$ ). Here again, the sensitivity analysis measured negative significant associations of

211 Simpson index with the frequency of mutations with NCA effects (PRCC,  $r=-0.372$ ,  $p<2.2\cdot 10^{-16}$ ) as  
212 well as with the range of mutation effects ( $r=-0.041$ ,  $p=4.2\cdot 10^{-2}$ , Supporting information, Tab. S3).  
213 We also simulated 2500 tumors until they reached  $3\cdot 10^5$  cells, in both fitness landscapes. In a tight  
214 fitness landscape, we also found a negative association of Simpson index with the frequency of  
215 mutations with NCA effects (Fig. 2C, linear regression:  $\log[\text{Simpson index}] = -5.33\pm 0.22 f_{NCA}$ ,  
216  $t=-23.69$ ,  $p<2.2\cdot 10^{-16}$ ,  $R^2=0.183$ ). The sensitivity analysis supports this relationship with the  
217 frequency of mutations with NCA effects (PRCC,  $r=-0.388$ ,  $p<2.2\cdot 10^{-16}$ ), but also measured a  
218 positive significant association with the range of mutation effects ( $r=0.055$ ,  $p=6.0\cdot 10^{-3}$ , Supporting  
219 information, Tab. S3). However, in a wide fitness landscape, Simpson index increases with the  
220 frequency of mutations with NCA effects between 0% and 12.5% of mutations with NCA effects  
221 (Fig. 2D, linear regression:  $\text{Simpson index} = 0.31\pm 0.09 f_{NCA}$ ,  $t=3.46$ ,  $p=5.7\cdot 10^{-4}$ ,  $R^2=0.011$ ).  
222 Above 12.5%, Simpson index does not significantly vary with the frequency of mutations with  
223 NCA effects. Though, the sensitivity analysis does not support this relationship, and measured a  
224 negative significant association of Simpson index with the frequency of mutations with NCA effects  
225 (PRCC,  $r=-0.057$ ,  $p=4.2\cdot 10^{-3}$ ). It also measured positive significant associations with the range of  
226 mutation effects ( $r=0.052$ ,  $p=8.7\cdot 10^{-3}$ ), as well as the basal division rate (ranging from  $4\cdot 10^{-3}$  to  $6\cdot 10^{-3}$ ,  
227  $r=0.043$ ,  $p=3.1\cdot 10^{-2}$ ) and the mutation rate (ranging from  $8\cdot 10^{-5}$  to  $1.2\cdot 10^{-4}$ ,  $r=0.046$ ,  $p=2.1\cdot 10^{-2}$ ,  
228 Supporting information, Tab. S3).  
229



230

231 **Figure 2: Impacts of NCA effects on tumor diversification.** 500 simulations were performed for each  
 232 condition with the following parameters:  $N_0=10000$ ,  $b_0 = d_0 \in [4 \times 10^{-3}, 6 \times 10^{-3}]$ ,  $t_{max}=300$ ,  $N_{max} = 30 N_0$ ,  
 233  $r_{max} \in [1.6 b_0, 2.4 b_0]$ ,  $b_{max} = d_{max} = 5 r_{max}$ ,  $\mu \in [8 \times 10^{-5}, 1.2 \times 10^{-4}]$ ,  $\sigma \in [0.8, 1.2]$  and  $\alpha_t \in [2.4, 3.6]$ . Simpson  
 234 index is displayed in light blue, and linear regressions in red. (A) Simulations performed during 300 generations for a  
 235 tight fitness landscape (linear regression,  $R^2=0.208$ ). (B) Simulations performed during 300 generations for a wide  
 236 fitness landscape (linear regression,  $R^2=0.147$ ). (C) Simulations performed until the tumor reaches  $3 \cdot 10^5$  cells for a tight  
 237 fitness landscape (linear regression,  $R^2=0.183$ ). (D) Simulations performed until the tumor reaches  $3 \cdot 10^5$  cells for a wide  
 238 fitness landscape (linear regression,  $R^2=0.011$ ).

239

240

### 241 3.2 Impacts of NCA effects on tumor growth kinetics

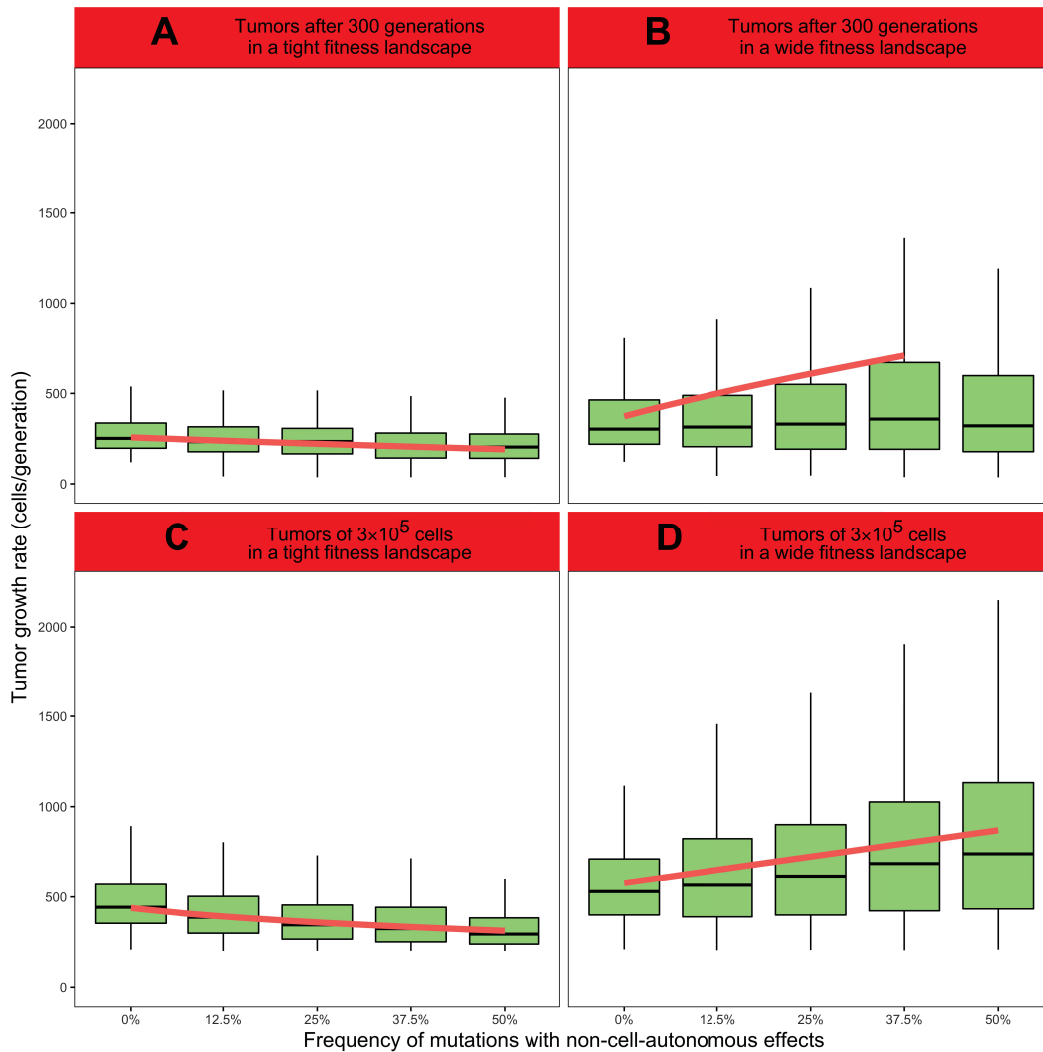
242 We measured tumor growth rate as an index of tumor growth kinetics for the tumors simulated in a  
243 tight fitness landscape. For tumors simulated during the same amount of time in a tight fitness  
244 landscape, tumor growth rate is negatively associated with the frequency of mutations with NCA  
245 effects increases (Fig. 3A, linear regression:  $\log[\text{Tumor growth rate}] = -0.59 \pm 0.05 f_{NCA}$ ,  $t = -$   
246  $11.02$ ,  $p < 2.2 \cdot 10^{-16}$ ,  $R^2 = 0.046$ ). The sensitivity analysis supports this negative association with the  
247 frequency of NCA effects (PRCC,  $r = -0.221$ ,  $p < 2.2 \cdot 10^{-16}$ ), but tumor growth rate is also significantly  
248 positively associated with minimal tumor size ( $r = 0.278$ ,  $p < 2.2 \cdot 10^{-16}$ ), as well as with the basal  
249 division rate ( $r = 0.178$ ,  $p < 2.2 \cdot 10^{-16}$ ) and the range of mutation distribution ( $r = 0.376$ ,  $p < 2.2 \cdot 10^{-16}$ ,  
250 Supporting information, Tab. S4). Conversely, in a wide fitness landscape, tumor growth rate is  
251 positively associated with the frequency of mutations with NCA effects (Fig. 3B, linear regression:  
252  $\sqrt{\text{Tumor growth rate}} = 11.88 \pm 1.60 \sqrt{f_{NCA}}$ ,  $t = 7.41$ ,  $p = 1.9 \cdot 10^{-13}$ ,  $R^2 = 0.026$ ). Above 37.5%, tumor  
253 growth rate does not significantly vary with the frequency of mutations with NCA effects. This  
254 positive association with the frequency of mutations with NCA effects is confirmed by the  
255 sensitivity analysis (PRCC,  $r = 0.077$ ,  $p = 1.1 \cdot 10^{-4}$ ). The sensitivity analysis also measured significant  
256 positive associations with minimal tumor size ( $r = 0.175$ ,  $p < 2.2 \cdot 10^{-16}$ ), as well as with the basal  
257 division rate ( $r = 0.136$ ,  $p = 7.4 \cdot 10^{-12}$ ), and the range of mutation distribution ( $r = 0.146$ ,  $p = 2.3 \cdot 10^{-13}$ ,  
258 Supporting information, Tab. S4).

259 For tumors simulated until reaching the same size in a tight fitness landscape, tumor growth rate is  
260 negatively associated with the frequency of mutations with NCA effects (Fig. 3C, linear regression:  
261  $\log[\text{Tumor growth rate}] = -0.48 \pm 0.03 \sqrt{f_{NCA}}$ ,  $t = -17.53$ ,  $p < 2.2 \cdot 10^{-16}$ ,  $R^2 = 0.109$ ). The sensitivity  
262 analysis supports this negative relationship with the frequency of NCA effects (PRCC,  $r = -0.453$ ,  
263  $p < 2.2 \cdot 10^{-16}$ ), and also measured significantly positive associations with minimal tumor size  
264 ( $r = 0.134$ ,  $p = 2.1 \cdot 10^{-11}$ ), the basal division rate ( $r = 0.184$ ,  $p < 2.2 \cdot 10^{-16}$ ), and the range of mutation  
265 distribution ( $r = 0.416$ ,  $p < 2.2 \cdot 10^{-16}$ , Supporting information, Tab. S4). In a wide fitness landscape,  
266 tumor growth rate increases with the frequency of mutations with NCA effects (Fig. 3D, linear

267 regression: Tumor growth rate =  $585.42 \pm 47.55 f_{NCA}$ ,  $t=12.31$ ,  $p < 2.2 \cdot 10^{-16}$ ,  $R^2=0.057$ ). This  
268 positive association with the frequency of mutations with NCA effects is confirmed by the  
269 sensitivity analysis (PRCC,  $r=0.195$ ,  $p < 2.2 \cdot 10^{-16}$ ), which also measured significant positive  
270 associations with minimal tumor size ( $r=0.128$ ,  $p=1.5 \cdot 10^{-10}$ ), the basal division rate ( $r=0.146$ ,  
271  $p=2.3 \cdot 10^{-13}$ ), and the range of mutation distribution ( $r=0.117$ ,  $p=4.0 \cdot 10^{-9}$ , Supporting information,  
272 Tab. S4).

273 We globally measured a significant negative association between Simpson index and tumor growth  
274 rate when tumors were simulated in a wide fitness landscape, but no correlation for a tight fitness  
275 landscape (Supporting information, Tab. S5 and Fig. S2).

276



277

278 **Figure 3: Impacts of NCA effects on tumor progression.** 500 simulations were performed for each  
 279 condition with the following parameters:  $N_0=10000$ ,  $b_0 = d_0 \in [4 \times 10^{-3}, 6 \times 10^{-3}]$ ,  $t_{max}=300$ ,  $N_{max} = 30 N_0$ ,  
 280  $r_{max} \in [1.6 b_0, 2.4 b_0]$ ,  $b_{max} = d_{max} = 5 r_{max}$ ,  $\mu \in [8 \times 10^{-5}, 1.2 \times 10^{-4}]$ ,  $\sigma \in [0.8, 1.2]$  and  $\alpha_t \in [2.4, 3.6]$ . Tumor  
 281 growth rate is displayed in light green, and linear regressions in red. Outliers of tumor growth rate distribution are not  
 282 displayed. (A) Simulations performed during 300 generations for a tight fitness landscape (linear regression,  $R^2=0.046$ ).  
 283 (B) Simulations performed during 300 generations for a wide fitness landscape (linear regression,  $R^2=0.026$ ). (C)  
 284 Simulations performed until the tumor reaches  $3 \cdot 10^5$  cells for a tight fitness landscape (linear regression,  $R^2=0.109$ ). (D)  
 285 Simulations performed until the tumor reaches  $3 \cdot 10^5$  cells for a wide fitness landscape (linear regression,  $R^2=0.057$ ).

286

287

288 **4. Discussion**

289 For a tight fitness landscape, *i.e.* when CA and NCA effects mix up to impact the division and death  
290 rates, frequent NCA effects are associated to lower CD (cf. Fig. 2A and 2C). For a wide fitness  
291 landscape, *i.e.* when NCA effects extend the range of potential impacts of mutations on clonal  
292 growth rates, the relationship between NCA effects and CD is the same only when tumors grow  
293 during a fixed number of generations (Fig. 2B). This negative relationship is confirmed by the  
294 sensitivity analysis, where the partial rank correlation between CD and the frequency of NCA  
295 effects is systematically negative (Supporting information, Tab. S3). We could also measure the  
296 opposite relationship (*i.e.*, when frequent NCA effects yield higher CD, Fig. 2D) for tumors  
297 growing until a fixed size, but only for low frequencies (0 to 12.5%) of mutations with NCA effects,  
298 and in contradiction with the sensitivity analysis (Tab. S3). We suspected this latter positive  
299 relationship to depend on each tumor's size: it was only observed when all the simulations  
300 (2500/2500) yielded tumors larger than  $3 \cdot 10^5$  cells, while the negative relationship could be  
301 observed for smaller tumors (*e.g.*, Fig. 2B: 407/2500 simulations yielded tumors larger than  $3 \cdot 10^5$   
302 cells). Yet, we still observed a negative relationship between NCA effects and CD when performing  
303 the same analysis on the sample of tumors larger than  $3 \cdot 10^5$  cells (Supporting information, Fig. S3).  
304 Moreover, tumors growing until a fixed size could evolve during a wider timeframe (88 to 1492  
305 generations) than tumors growing during a fixed number of generations (300 generations): this  
306 configuration could render the positive relationship between CD and NCA effects risky to interpret.  
307 Thus, we will not discuss these results any further, and we suggest that NCA effects and CD should  
308 generally have a negative relationship, regardless of the fitness landscape considered. Besides, the  
309 relationship between tumor growth and NCA effects strongly depends on the fitness landscape:  
310 frequent NCA effects generate lower tumor growth rate in a tight fitness landscape (Fig. 3A and 3C,  
311 Supporting information, Tab. S4), but higher tumor growth rate in a wide fitness landscape (Fig. 3B  
312 and 3D, Supporting information, Tab. S4). Moreover, though we found no association between  
313 tumor growth rate and Simpson index for tumors simulated in a tight fitness landscape (Supporting



314 information, Tab. S4 and Fig. S2A and S2C), high CD is associated with slow tumor growth  
315 kinetics in tumors simulated in a wide fitness landscape (Tab. S4 and Fig. S2B and S2D).

316 In a tight fitness landscape, CA effects can be the main component of clonal growth kinetics. Thus,  
317 neutral mutations arising in the fastest growing clones give birth to a large range of similarly  
318 growing clones that can coexist and maintain CD at a high level (cf. Fig. 4A, considering that  
319 neutral mutations give rise to phenotypic changes that are unrelated to growth kinetics). This higher  
320 CD can be mitigated by the emergence of mutations with detrimental NCA effects, that can slow  
321 down clonal growth kinetics. Due to the tight bounds of the fitness landscape, these detrimental  
322 impacts are quite difficult to be balanced by beneficial NCA effects (cf. Fig. 4B). In this context,  
323 tumors are therefore likely to grow faster without NCA effects, and the contribution of NCA effects  
324 is therefore detrimental to CD.

325 In a wide fitness landscape, NCA effects can be the main component of clonal growth kinetics over  
326 the impacts of CA effects. In this context, many mutations are likely to shift the sensitivity of the  
327 latest clones to NCA effects. Similarly growing clones are therefore unlikely to coexist in this  
328 context, which significantly impairs cooperation and promotes competition between clones. Thus,  
329 beneficial NCA effects can not only support the growth of predominant clones already benefitting  
330 from their beneficial CA effects, but also allow clones undergoing their detrimental CA effects to  
331 persist in the tumor. Similarly, detrimental NCA effects can both slow down the growth of the  
332 predominant clones and speed up the extinction of the slowest growing ones (cf. Fig. 4D). In this  
333 context, we found a negative relationship between CD and tumor growth kinetics, which could  
334 indicate that NCA effects mainly drive the growth of predominant clones (cf. Fig. 4D), thus  
335 lowering CD.

336 Our model predicts not only that NCA effects do not drive tumors to high CD, but also that they  
337 impair the increase of CD, by shaping the growth rates of preexisting and emerging clones. This  
338 pattern is clearly not expected, considering that all previous observations and discussions on the  
339 impacts of NCA effects on CD have supported the hypothesis that NCA effects should promote

340 CD.<sup>20-23,25,40-44</sup> However, these results have been observed either in vitro<sup>44</sup> or in tumor grafts or  
341 xenografts,<sup>20-22,40-43</sup> and thus have not embraced the whole complexity of possible interactions  
342 within a tumor.<sup>25,45</sup> These studies have simultaneously considered two clones carrying mutations  
343 with NCA effects or less, most of the time in established tumors. Conversely, our model  
344 theoretically allows considering up to 50% of clones carrying mutations with NCA effects among  
345 large mixtures of clones, in tumors that expand unrestrictedly. Therefore, though NCA effects may  
346 support coexistence for a few clones in established tumors, our results tend to show that this would  
347 not be the case when larger assemblages emerge over a short time interval, as is common during  
348 carcinogenesis.<sup>36,46,47</sup> It is yet to note that our results only regard early (because small-sized),  
349 expanding tumors (or expanding tumor niches), and that our model may yield different results for  
350 larger cancer cell populations and/or higher numbers of generations.

351 These differences between our results and previous observations could be explained by an increase  
352 of competition when NCA effects are very frequent. Indeed, by shaping the growth kinetics of  
353 various clones, CA and NCA effects contribute to establish a network of biological interactions  
354 between clones.<sup>21,44</sup> Biological interactions have been widely studied in ecology and evolution to  
355 explain the respective impacts of different species on each other's growth,<sup>48</sup> ranging from  
356 competition (mutually detrimental) to mutualism (mutually beneficial), and their impacts on cancer  
357 progression have been increasingly pointed out due to the many similarities between tumors and  
358 wild ecosystems.<sup>23,25,45,49</sup> Here, detrimental NCA effects may be considered as interference  
359 competition, since cancer cells can remotely suppress each other's growth.<sup>50</sup> Competition events  
360 were shown to yield a drop of CD.<sup>19</sup> On the contrary, mutualistic and commensalistic interactions,  
361 which can be involved through beneficial NCA effects, can promote the coexistence of several  
362 clones.<sup>20,41,42,44,49,51</sup> Though, when beneficial NCA effects depend on the relative abundances of  
363 clones (which is not the case here), they behave like limited resources and can result in other forms  
364 of exploitation competition.<sup>21,44,51,52</sup>

365 The relationship that we found between NCA effects, clonal growth kinetics and CD can be put in

366 perspective of clinical data. Indeed, our results forecast that, when NCA effects have distinct  
367 impacts on clonal growth rates from CA effects', the slowest growing tumors should be the most  
368 clonally diverse after a given amount of time. Indeed, when clinically detected, tumors mostly  
369 composed of slowly-dividing cancer cells are generally described as heterogeneous<sup>9</sup> and  
370 aggressive,<sup>53</sup> while fast-growing tumors usually well respond to treatments.<sup>54</sup> However, the link  
371 between tumor growth kinetics and ITH was mostly established for tumors of clinical size, often  
372 after several years under various regimens of selection,<sup>55</sup> and our results predict these  
373 heterogeneous, slow growing tumors to occur when mutations with NCA effects are rare. This could  
374 be the reason why so few mutations with NCA effects have been described so far. Moreover, if  
375 NCA effects may have a limited contribution to growth kinetics of clinical-stage tumors, there are  
376 evidence that NCA effects can significantly contribute to early carcinogenesis.<sup>29,56,57</sup> Further studies  
377 should therefore investigate tumor growth kinetics at early stages, in order to clearly identify the  
378 contribution of NCA effects to ITH.

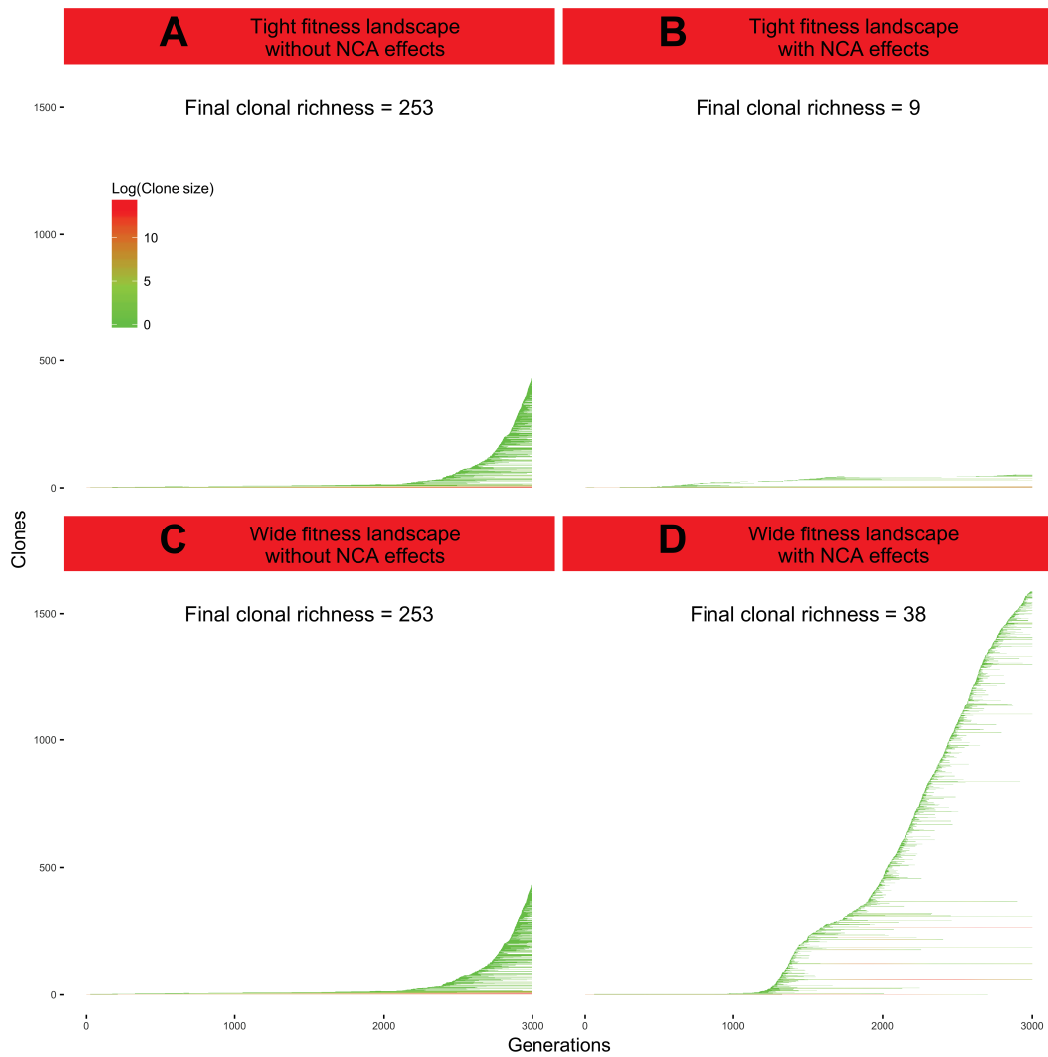
379 The design of this model mainly aimed at providing a framework to investigate the  
380 underappreciated impact of NCA effects on ITH.<sup>58</sup> Though, for the sake of simplicity, we made  
381 several assumptions that deserve to be discussed and further investigated. In this model, we  
382 assumed that divisions always occurred before death events. However, the order of birth and death  
383 events may have large impacts on the outcome of discrete eco-evolutionary processes (especially in  
384 the evolution of interactions)<sup>59</sup>, and results might thus differ for further studies considering other  
385 division and death orders. Moreover, the contribution of NCA effects to a clone's growth kinetics do  
386 not depend on any clone's size: *i.e.*, NCA effects are not limiting factors. Some NCA effects rely on  
387 widely secreted metabolites<sup>50,60-62</sup> or on the extensive recruitment of stromal cells,<sup>21,63</sup> and should be  
388 well described by this model. Others might be under frequency-dependent selection,<sup>20,44</sup> but their  
389 incidence in tumors has not been established. Furthermore, we assumed that factors involving NCA  
390 effects (*e.g.*, growth factors, miRNAs) diffuse instantly from one cell to another, which is rarely  
391 encountered *in vitro* and *in vivo*.<sup>28,44,61</sup> Diffusion constraints should play a significant role in shaping

392 CD, either directly by selecting a range of interacting partners,<sup>44</sup> or indirectly by shaping the growth  
393 kinetics,<sup>28</sup> or even by allowing the construction of spatially distinct niches simultaneously  
394 dominated by different clones.<sup>23</sup> Though, this model only encompasses up to  $10^7$  cells (see section  
395 2.2) at the same time, which should correspond to  $0.01\text{--}0.1\text{ mm}^3$  *in vivo*:<sup>64</sup> we can therefore easily  
396 assume that the diffusion time is negligible before the average cell cycle duration. Stromal cells  
397 involved in some NCA effects should also spread quickly at such scales.<sup>21,63</sup> Besides, tumors are  
398 very spatially heterogeneous<sup>65</sup> and the ME usually consists of several niches that may sparsely  
399 interfere with each other, so that we can easily assume this model to describe the cell dynamics at  
400 stake in the local ME. Tumors of clinic size actually gather several billions of cells in  
401 average,<sup>64,66</sup> and this model could thus be nested in wider-scale models of tumor dynamics. Finally,  
402 it is to note the impacts of NCA effects on tumor growth kinetics have been very sparsely  
403 quantified. Thus, we do not know whether up to 50% of mutations arising during cancer  
404 progression might have NCA effects, which is something crucial to quantify.

405 Since ITH is usually a good proxy for cancer aggressiveness and post-therapeutic recurrence at  
406 clinical stages,<sup>2,4-7</sup> a major challenge in cancer research is to better predict the evolution of  
407 phenotypic diversity in a patient's tumor. In this study, we have pointed out the possibility to  
408 identify a range of selection regimens during tumor growth, in which various mutational landscapes  
409 contribute to shape CD in the tumor. Notably, we found that when NCA effects made little  
410 contribution to growth kinetics, CD was the highest for the fastest growing tumors. Conversely,  
411 when NCA effects made significant contribution to growth kinetics, CD was the highest for the  
412 slowest growing tumors. Such theoretical predictions could allow new perspectives in the prediction  
413 of each patient's ITH. Indeed, ITH is well-documented for some cancers for which aggressiveness  
414 strongly depends on phenotypic diversity (e.g. glioblastoma multiforme<sup>14,67</sup>), and growth kinetics of  
415 such cancers are monitored for clinical stages. Nevertheless, though their contributions to shaping  
416 the ME are widely studied, the emergence of mutations with NCA effects is still poorly understood  
417 and should call for a systematic identification of these mutations in order to predict the tumor's

418 outcome.

419



420

421 **Figure 4: Emergence of new clones across time.** Each panel displays the monitoring of a simulation during

422 3000 generations. (A) Simulation of branching evolution in a tumor with no NCA effect and a tight fitness landscape.

423 (B) Simulation of branching evolution in a tumor with 100% of mutations with NCA effects and a tight fitness

424 landscape. (C) Simulation of branching evolution in a tumor with no NCA effect and a wide fitness landscape. (D)

425 Simulation of branching evolution in a tumor with 100% of mutations with NCA effects and a wide fitness landscape.

426

427

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568 **Author contributions statement**

569 TT conceived the study, designed the study, designed the model, carried out the statistical analyses  
570 and drafted the manuscript; BR coordinated the study, helped design the model, helped carry out the  
571 statistical analyses and helped draft the manuscript; FT helped draft the manuscript. All authors  
572 gave final approval for publication.

573

574 **Data availability statement**

575 No datasets were generated or analysed during the current study.

576

577 **Competing interests**

578 TT, FT and BR declare no financial or non-financial competing interests.

## Partie III

# Le cancer comme pression de sélection

L'apparition d'une mutation lors d'une division cellulaire n'a pas forcément d'effet sur le devenir d'une lignée : portée par une lignée somatique, elle influencera le phénotype du porteur ; portée par la lignée germinale, elle influencera le phénotype du porteur, mais également celui de ses descendants. Parmi les mutations germinales, la grande majorité ne modifie pas non plus la survie et la fécondité de ses porteurs : beaucoup ne portent pas sur une séquence codante, sont compensées par la redondance du code génétique, ou portent sur des domaines non essentiels à la fonction des protéines encodées. Seule une faible proportion des mutations peut en fait influencer sa propre transmission : positivement ou négativement selon son effet sur le phénotype du porteur. Néanmoins, un allèle ne fonctionne jamais seul : les interactions intra- ou inter-locus au sein du génome, et l'expression différentielle selon l'environnement, participent à influencer l'effet d'un allèle sur la survie et la fécondité de l'organisme.

Ainsi, de nombreux allèles portés par la lignée germinale sont susceptibles de moduler la probabilité qu'une cellule de l'organisme devienne cancéreuse. Certains ont un effet anti-oncogénique (caretakers, gatekeepers, etc.) et peuvent donc être soumis à sélection positive, mais d'autres peuvent au contraire avoir un effet pro-oncogénique. Ces allèles pro-oncogéniques devraient réduire la fécondité et/ou la survie des individus qui les portent, et donc être maintenus à l'équilibre mutation-sélection dans les populations. Plusieurs hypothèses expliquent la persistance de certains de ces allèles à des fréquences plus élevées : notamment, certains allèles ont des effets pléiotropes, et d'autres ne sont exprimés que dans des périodes où la fécondité des individus est moindre. Néanmoins, certains allèles pro-oncogéniques favorisent l'apparition de cancers relativement tôt, sans avoir d'effets bénéfiques pour la fécondité de l'individu.

Dans ce chapitre, je propose une hypothèse complémentaire pour expliquer le maintien d'allèles pro-oncogéniques héréditaires au dessus de l'équilibre mutation-sélection. Le cancer est un phénomène progressif, et ses effets sur la valeur sélective individuelle ne prennent leur ampleur qu'aux stades cliniques. L'interaction des allèles pro-oncogéniques avec des locus anti-oncogéniques est susceptible de suffisamment ralentir la progression cancéreuse pour que ses effets délétères ne s'expriment qu'en période post-reproductive. Cette interaction neutraliserait les effets délétères des allèles pro-oncogéniques, et les autoriserait à se maintenir dans les populations à l'équilibre mutation-dérive. Cette hypothèse est discutée dans la section 7, et suivie d'une courte exploration théorique dans la section 8.

## 7 Evolution des cancers familiaux : une approche neutraliste

**Titre :** *The guardians of inherited oncogenic vulnerabilities*

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# The guardians of inherited oncogenic vulnerabilities

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Similar to seemingly maladaptive genes in general, the persistence of inherited cancer-causing mutant alleles in populations remains a challenging question for evolutionary biologists. In addition to traditional explanations such as senescence or antagonistic pleiotropy, here we put forward a new hypothesis to explain the retention of oncogenic mutations. We propose that although natural defenses evolve to prevent neoplasm formation and progression thus increasing organismal fitness, they also conceal the effects of cancer-causing mutant alleles on fitness and concomitantly protect inherited ones from purging by purifying selection. We also argue for the importance of the ecological contexts experienced by individuals and/or species. These contexts determine the locally predominant fitness-reducing risks, and hence can aid the prediction of how natural selection will influence cancer outcomes.

**KEY WORDS:** Cancer, natural defenses, purifying selection, somatic mutations.

The “war on cancer” commenced more than half a billion years ago with the evolution of multicellular organisms (Nunney 2013). Indeed, at the dawn of Metazoans, cancer suppression represented a significant selection advantage to those individuals who were able to control unregulated cell division over those who were not

(Aktipis and Nesse 2013). Although most cancer-causing mutant alleles are somatically acquired during a lifetime (thereafter SCMA for somatic cancer-causing mutant allele), certain cancers are caused by congenital mutations, that is, germinally inherited cancer-causing mutant alleles (ICMA; Table 1). Why has evolution not done a “better job” at eliminating them? In spite of several studies on the topic, it is still not clear whether most ICMA, like

\*Both authors contributed equally to this work.

**Table 1.** The three types of genes that are known to play a role in cancer susceptibility.

Gene types	Mutation types	Genes	Example of cancer susceptibility (syndrome or main tumor type)	References
Proto-oncogenes	Inherited	Ret XMRK	MEN II Melanoma (fish)	Huang et al. (2000), Fernandez and Morris (2008), Fernandez and Bowser (2010)
	Acquired	K Ras HER2 Braf EGFR	Colon Breast Melanoma Lung	Giampuzzi et al. (2001), Paez et al. (2004), Geyer et al. (2006), Thomas et al. (2007)
Tumor suppressor genes	Inherited	APC P53 Rb PTEN	Familial adenomatous polyposis Li Fraumeni Retinoblastoma Breast	Bandara and La Thangue (1991), Lal and Gallinger (2000), Nochols et al. (2001), Zhou et al. (2007)
	Acquired	P53 APC PTEN	Breast, lung, ovary, colon . . . Colorectal Prostate	Fodde et al. (2001), Nochols et al. (2001), Wang et al. (2003)
DNA repair genes	Inherited	XPA, XPB, XPC, XPD BRCA1, BRCA2 hMLH1, hMSH2, hMSH6 ATM PalB2	Xeroderma pigmentosum Breast, ovary Colon, uterus Breast Breast	Grady et al. (2001), Antoniou et al. (2003), Renwick et al. (2006), Tischkowitz et al. (2007), Feltes and Bonatto (2014)
	Acquired	hMLH1, hMSH2 BRCA1, BRCA2	Colon Ovary	Grady et al. (2001), King et al. (2003)

A proto-oncogene is a normal gene that can become an oncogene due to mutations or increased expression. When this happens, the cell grows out of control, which can lead to cancer. Tumor suppressor genes are normal genes that slow down cell division, repair DNA mistakes, or tell cells when to die (a process known as apoptosis or programmed cell death). When tumor suppressor genes do not work properly, cells can grow out of control, which can lead to cancer. DNA repair genes are genes linked to the recognition and repair of damaged DNA. Defects in these genes enable cancer cells to accumulate genomic alterations that contribute to their aggressive phenotype (see <http://www.cancer.org/acs/groups/cid/documents/webcontent/002550-pdf.pdf>).

any rare disadvantageous mutation, are maintained at levels predicted by mutation–selection balance (Nunney 2003) and/or are maintained by selection (potentially at a higher frequency than that expected; see Bodmer 2006; Risch et al. 2006). Recent advances in evolutionary medicine have highlighted that ICMA, similar to other maladaptive mutations, can in fact be maintained in populations through various processes. For instance, it has been suggested that natural selection is unlikely to act on ICMA when their detrimental effects occur after the reproductive life (Nunney 2003; Frank 2004). In addition, antagonistic pleiotropy (the expression of a gene resulting in multiple competing effects) might be important if late acting oncogenic mutations, including inherited ones, have beneficial effects at younger ages (Boddy et al.

2015). For example, in *Xiphophorus* fish, melanoma-promoting oncogene alleles are associated with larger body size and aggressiveness and confer early life advantages in male–male competition and female mate choice (see Fernandez and Morris 2008; Fernandez and Bowser 2010). Women with *BRCA1/2* mutations have a significantly higher lifetime risk of developing breast or ovarian cancer, but elevated fertility of mutation carriers indicates that these women are also more fecund despite their elevated postreproductive mortality risks (Smith et al. 2012). It has also been suggested that the maintenance of ICMA can be a by-product of genomic conflict (“selfish” genes: Kleene 2005) and/or antagonistic coevolution (e.g., maternal–fetal interactions; Summers and Crespi 2005). Also, when ICMA are rare, their purge by

natural selection is slow and/or difficult, and this may explain why they persist in natural populations. Finally, ICMA can be present due to being caused by recent germline mutations for which insufficient time has passed to remove them from gene pools.

In this article, we aim to highlight the paradoxical role of natural protective mechanisms that not only guard organisms from cancer, but on the other hand, also protect ICMA from being counterselected by alleviating their detrimental effect on fitness. Additionally, we argue that ecological contexts experienced by individuals and/or species are crucial to be considered because they could potentially determine locally occurring fitness-reducing risk factors (e.g., somatic diseases related to aging, parasite infections, predation, or adverse environmental conditions), and hence also influence the intensity with which natural selection will be acting on both tumor burden and ICMA.

### *Natural Cancer Prevention Mechanisms Potentially Protecting ICMA*

Natural selection has favored a variety of heritable adaptations that either prevent the formation of neoplasms or control their growth and progression (Nunney 1999). The defense mechanisms against cancer therefore fall into two conceptually different components: (1) the ability to eliminate tumors and (2) the ability to limit their proliferative potential (DeGregori 2011). Although both somatic defense (how cells avoid becoming malignant) and broader intrinsic defenses (cancer avoidance at the level of tissues and the whole organism) have the potential to suppress cancer and the associated detrimental consequences, they do not however eliminate, nor cure SCMA and ICMA. Because of the typically slow progression of malignancy, evolution's solutions against cancer are rather similar to those used in therapeutic strategies: both targeting symptoms rather than sources, and therefore rendering selection "myopic" to the mutations responsible for the disease. Recent studies based on autopsies of individuals who died of unrelated causes confirm that during our lifetime most of us steadily accumulate benign in situ tumors that do not necessarily lead to the development of malignant cancers (Folkman and Kalluri 2004). This supports the idea that evolutionary processes have been acting to suppress cancers occurring in prereproductive life by preventing tumors from becoming fatal, rather than by eliminating SCMA and ICMA.

Natural selection is not always "myopic" to germinally inherited deleterious mutations. For instance Duchenne muscular dystrophy is an X-linked muscular dystrophy for which there is currently no treatment to prevent or arrest the progressive muscle weakness. It affects one in 3500 male live births and patients rarely survive beyond their teens as the condition also causes progressive respiratory muscle weakness and respiratory failure (Eagle et al.

2002). Not surprisingly, because the disease sufferers generally do not survive to reproductive age, selective purging takes place and the prevalence of Duchenne muscular dystrophy remains low in human populations. Other examples could include Fanconi anemia (Kutler et al. 2003; Meetei et al. 2003), Bloom syndrome (Hickson et al. 2004) and ataxia telangiectasia (Domazet-Loso and Tautz 2010), diseases which all affect the sufferers prior to reaching reproductive age.

The reasons why natural selection tends to eliminate disease-causing genes in certain situations (e.g., Duchenne muscular dystrophy) and instead favors compensatory mechanisms that hide their deleterious effects in other instances (e.g., cancer) is explained by the evolutionary history of the pathology. Rare deleterious alleles do not promote compensation; however, common alleles that are initially neutral (or even advantageous) that become disadvantageous due to changing conditions may result in compensatory evolution.

Contrary to many genetic disorders, uncontrolled cell growth is a pathological manifestation that is concurrent with the dawn of multicellularity, it can even be viewed as an ancestral challenge for building viable multicellular organisms (Nunney 1999). Indeed cancer has been with us ever since multicellular organisms evolved. The emergence of proto-oncogenes facilitated cell cooperation by coordination, while the evolution of tumor suppressor genes kept tight control on cheater cells, contributing fundamentally to the establishment of stable multicellularity (Domazet-Loso and Tautz 2010). However, proper operation of multicellular organisms requires a constant balancing of such genes and precise regulation of overall cell proliferation levels and cell numbers (Leroi et al. 2003).

The evolution of ICMA is constrained by the effects on their bearers. If ICMA cause cancer while their bearers are still reproductive, they may impair the reproduction of their carriers, and therefore impair their own transmission. But if their oncogenic effect is delayed until after reproduction has ceased due to other causes (e.g., senescence, death, or diseases), then they have no effect on the individual's fitness, and can be passed on to the offspring. As tumor suppressor genes slow down cancer progression, but are progressively inactivated by somatic mutations, the more effective they are early in life, the later cancer will arise in the organism. Therefore, ICMA can be further passed on when compensatory mechanisms (such as tumor suppressor genes, immune system) are able to mask their oncogenic effects until a postreproductive period.

The concealment of oncogenic phenotypes likely explains why natural selection did not *only* systematically eliminate individuals with alleles causing uncontrolled cell proliferation (both SCMA and ICMA) prior to the end of reproduction, but also favored individuals that were able to keep developing malignancies under control and below the detrimental thresholds. Cancers

that are controlled to grow slowly enough not to endanger hosts within the time frame when natural selection can be effective, are not per se decreasing fitness. Individuals who could tolerate the early stages of late-acting cancers without suffering significant fitness reduction were then likely to be favored by selection over those unable to activate compensatory mechanisms.

ICMA (at least highly penetrant ones) are actually a direct cause of only a small proportion of cancers. Because most cancers instead originate from SCMA, it could be predicted that cancer preventing selective pressures were/are mostly directed toward tumor growth. This may be the reason why natural selection presumably favored compensatory mechanisms (at least against those oncogenic mutations that were not purged during the course of evolution). If this process has, from a human individual health perspective, the desirable effect to prevent cancer progression due to SCMA and ICMA, it will also have the undesirable effect of protecting ICMA, that is, the mutation–selection balance shifts so that a higher frequency of oncogenic alleles results (Nunney 2003). If this reasoning is correct, other genetic diseases initiated by both acquired and inherited mutations could face the same challenge: as soon as acquired mutations induce the disease with sufficient frequency, selection will favor compensatory mechanisms that in return protect abnormal genes/alleles from being eliminated across generations.

Therapies against malignancies (as for other pathologies, e.g., Type I Diabetes) act in the same way because even those targeting mutated genes do not eliminate nor cure ICMA. Thus, ICMA responsible for cancer early in life, instead of being counterselected, will rather become neutral if therapies are efficient. It is also interesting to consider treatments targeting symptoms rather than sources, that self-medication against cancer in animals (see Vittecoq et al. 2015) also renders selection “myopic” to the genes responsible for the disease. The existence of self-medication could also help to understand the persistence across generations of ICMA in wildlife genomes.

### *Frequency and Diversity of Intrinsic and Extrinsic Fitness Limiting Factors*

Various internal and/or external factors influence the reproductive life span of individuals and species in natural environments (Thomas et al. 2004). As recently highlighted by Roche et al. (2012) and Vittecoq et al. (2013), cancer, depending on species/populations and/or their habitat, is a more or less likely cause of death. For instance, small rodents in nature may succumb to cancer, but only if they do not first die from any one of numerous other causes, such as predators, infectious diseases, environmental causes (e.g., floods, extreme temperatures), etc. For those species, selection on both oncogenic mutation elimination and on genes responsible for natural defenses against tumor emer-

gence/growth is expected to be strong on a shorter period of the life. Natural selection leads to different investments in longevity (and the avoidance of cancer and other diseases) to the extent that maximizes reproductive success. Thus, selection is expected to act to lower the incidence of cancer (and other manifestations of aging) only up to the age when most of these animals ceased reproduction or died from other causes (Hamilton 1966). In accordance with this statement, when in protective captive conditions species such as wild mice (*Mus musculus*) have elevated incidences of cancer (46%; Andervont and Dunn 1962). Thus, with respect to the predominating factors limiting fitness, different predictions can be made on how natural selection should adjust the levels of cancer resistance: either through defenses against tumor development and progression or through selecting against ICMA. Somatic diseases such as cancer are likely to be an important source of fitness variation between individuals mainly in stable, well-resourced, environments with low pathogen loads and low predation rates. Selection pressures to prevent the formation and uncontrolled growth of tumors prior to old age should then be the highest in those habitats. It is however unclear if this will lead to more and more sophisticated defenses against cancer or to direct selection against ICMA, or both. There are several animal species which potentially present examples for this scenario: for instance elephants (*Loxodonta africana*), whose large size makes them nearly invulnerable to predators as adults (Shoshani and Eisenberg 1982) possess 20 copies of the tumor suppressor TP53 gene (Belyi et al. 2010). Although, the increased number of TP53 gene copies in elephants (compared to other mammals) has been attributed to their elevated risk of cancer resulting from their body size, their increased longevity has probably been an even more important driver of increased cancer suppression. It is therefore probable that these genetic defenses against cancer have, at least partially, evolved because of the selective advantage conferred by resistance to somatic diseases in this animal with low predation risk (and hence extended life span). Other organisms, supporting the idea that ecological context rather than only body size extends life span, are long-lived rodents, that is, the naked mole rat (*Heterocephalus glaber*) and the (unrelated) blind mole rat (*Spalax* spp., Gorbunova et al. 2014). Naked mole rats have no known cancer, even in captivity (Kim et al. 2011). This rodent lives underground, digging intricate tunnel networks in which they have virtually no chance of falling to predation, and has evolved some unique anti-cancer defenses, including enhanced cell contact inhibition. The blind mole rat has evolved a unique trade-off, boosting the immune system's necrotic defense, by expanding and duplicating immune genes to attack cancer cells while apparently weakening the key mediators of the normal cell-shutdown defense, the tumor suppressor TP53 (Fang et al. 2014).

Thus, in the light of the ideas developed above, a crucial question is: Are there any ecological contexts that could favor



the purge of ICMA? Basically, our hypothesis suggests that perfect tumor suppression (which theoretically removes the effects of ICMA) is equivalent to elimination of ICMA from a population (which is of course impossible because of mutation). Because cancerous lesions contained by compensatory mechanisms generally trigger little to no fitness reduction, abolition of a postreproductive period could potentially contribute to the increased purging of ICMA. If individuals suffer from a cancer without impact on their lifetime reproductive output, that is, fitness, then ICMA do not cause any fitness reduction and are unlikely to be selected against. However, if postponed breeding and postreproductive care significantly increase the fitness of the organism, then even ICMA with late oncogenic expression will be detrimental to fitness and selected against. A converse strategy could consist of constraining selection on compensatory mechanisms. Indeed, compensatory mechanisms are associated with antagonistic effects. Notably, tumor suppression and anticancer immunity can be associated with severe trade-offs with reproduction, such as senescence (Campisi 2001), and they can even promote carcinogenesis when unregulated (Coussens and Werb 2002; Coppé et al. 2010). Oncogenic effects of ICMA could therefore be unmasked by contexts where compensatory mechanisms are no longer beneficial. Moreover, for ICMA to cause fitness reduction, they must cause death or impair reproduction before other factors. Thus, a mandatory condition of ICMA elimination is that the associated cancer is a significant cause of mortality before or during the reproductive period. This requires driving the multigenic mutation–selection equilibrium for the set of genes responsible for a given cancer to near zero (Nunney 2003). Therefore, future research should explore how the frequency of ICMA could depend on other fitness reduction processes (such as predation and diseases, accidents, and the somatic mutation rate) possibly by focusing on a limited range of wildlife species in different ecosystems.

### Concluding Remarks

More empirical data are needed to explore the extent to which ICMA have higher frequencies in natural populations than expected by mutation–selection balance. Mutation–selection balance predicts a link between the frequency of ICMA and their deleterious effects. Indeed, an important assumption involved in our hypothesis is that ICMA effects on fitness are not related to their frequency. Because some equivalence could exist between having few highly deleterious alleles or several less deleterious ones, this issue should be clarified with empirical data. Because large and/or long-lived organisms have evolved more tumor suppression mechanisms (since cancer risk increases with size/age), according to our hypothesis, it is expected that the frequency of ICMA is higher in those species. We encourage further research to empirically test this prediction, for example, in species such as

naked mole rats or elephants. Finally, a promising research direction will be to explore whether human populations experiencing a historically higher risk of cancer due to ecological conditions would have additional tumor suppression mechanisms and higher ICMA frequencies.

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## 8 Exploration théorique de l'approche neutraliste pour l'évolution des cancers familiaux

La section 7 suggère l'existence de conditions écologiques et d'espèces qui favorisent le maintien d'allèles pro-ongéniques dans les populations. Dans cette section, nous explorons cette hypothèse dans un cadre théorique, afin de déterminer sa plausibilité et son potentiel pour des recherches ultérieures. Dans un premier temps, nous proposons des équations modélisant l'impact du cancer sur la valeur sélective au cours de la vie de l'individu. Dans un second temps, nous utilisons ces équations pour tester si des allèles pro-oncogéniques peuvent être considérés comme neutres du point de vue de la sélection.

**Histoire de vie d'une espèce soumise au cancer** Nous nous intéressons ici à une population d'individus dont l'histoire de vie est divisée en deux périodes : d'une part, une période reproductive durant laquelle les individus assurent leur survie et leur reproduction ; d'autre part, une période post-reproductive durant laquelle les individus ne produisent plus le moindre descendant. Nous supposons que cette période reproductive démarre à la naissance de l'individu ( $t = 0$ ) et dure jusqu'à sa sénescence ( $t = T_{old} \geq 0$ ), et que la période post-reproductive démarre à la sénescence pour durer jusqu'à la mort de l'individu.

Cette espèce peut souffrir de lésions cancéreuses, lesquelles apparaissent tout au long de la vie de l'individu (Marion Vittecoq et al. 2013). Nous considérons qu'une tumeur a besoin de croître suffisamment pour nuire significativement à la santé de l'organisme. Aussi, les lésions cancéreuses n'ont aucun impact sur l'organisme jusqu'à ce qu'elles atteignent un seuil critique de lésions  $C_{critical}$ . Alors, à partir du moment  $T_{critical} \geq 0$  où les lésions atteignent ce seuil, nous considérons que les individus ne sont plus capables de se reproduire : soit qu'ils réallouent toutes leurs ressources à combattre le cancer, soit qu'ils sont déjà morts. Si ce stade critique de cancer est atteint après la période reproductive, il n'a aucun impact sur la reproduction ; mais si trop de lésions se produisent durant la période reproductive, celles-ci peuvent considérablement nuire à la valeur sélective de l'individu. Aussi, le paramètre  $w$  correspond au nombre moyen de descendants d'un individu par unité de temps, de sorte que la valeur sélective d'un individu peut s'écrire de la manière suivante :

$$W = w \text{Min}(T_{old}, T_{critical}) \quad (1)$$

Nous supposons que la quantité de lésions cancéreuses  $C$  dépend de l'équilibre entre l'activation des gènes proto-oncogènes  $Y$  et l'activation des gènes suppresseurs de tumeur  $Z$  :

$$C(Y, Z) = A e^{\frac{Y}{Z}}$$

où  $A > 0$  est une constante d'accumulation des lésions cancéreuses.

Dans les faits, chaque individu naît avec ses gènes proto-oncogènes et suppresseurs de tumeurs activés à un niveau initial : respectivement  $y \geq 0$  et  $z \geq 0$ . Ces niveaux d'activation initiaux  $y$  et  $z$  sont des caractères encodés au niveau génétique (héritables), portés par la lignée germinale, et pour lesquels plusieurs variants existent dans la population. Du fait des mutations somatiques se produisant aléatoirement au cours de la vie de l'individu, l'activation des proto-oncogènes augmente à un taux  $\alpha \geq 0$  et l'activation des gènes suppresseurs de tumeurs diminue à un taux  $\beta \geq 0$ . Par conséquent, ces deux taux changent de la manière suivante :

$$Y(t) = y + \alpha t$$

$$Z(t) = z - \beta t$$

et la quantité de lésions cancéreuses dans un individu à un instant donné est donc :

$$C(t) = A e^{\frac{y+\alpha t}{z-\beta t}}$$

Par conséquent, en fonction du seuil critique de lésions d'un individu  $C_{critical}$ , nous estimons l'âge moyen  $T_{critical}$  auquel le cancer a des effets cliniques sur l'individu.

$$\begin{aligned} C(T_{critical}) = C_{critical} &\leftrightarrow A e^{\frac{y+\alpha T_{critical}}{z-\beta T_{critical}}} = C_{critical} \\ &\leftrightarrow T_{critical} = \frac{-y + z \text{Log} \left[ \frac{C_{critical}}{A} \right]}{\alpha + \beta \text{Log} \left[ \frac{C_{critical}}{A} \right]} \end{aligned}$$

Dans cette population, il est donc possible de calculer la valeur sélective de n'importe quel individu, uniquement en fonction de ses deux caractères  $y$  et  $z$  :

$$W[y,z] = w \text{Max} \left[ 0, \text{Min} \left[ T_{old}, \frac{-y + z \text{Log} \left[ \frac{C_{critical}}{A} \right]}{\alpha + \beta \text{Log} \left[ \frac{C_{critical}}{A} \right]} \right] \right] \quad (2)$$

**Analyse résident-mutant** Nous considérons une population de taille infinie de l'espèce donnée, dans laquelle une stratégie résidente est à l'équilibre, et nous introduisons des mutants de cette stratégie un par un, jusqu'à trouver un résident qu'aucun mutant ne peut envahir (J Maynard Smith and G. R. Price 1973). Cette approche est valide sous l'hypothèse que les événements de mutation sont rares. Les populations résidentes sont mises en compétition avec un mutant à la fois, et de nouveaux mutants n'apparaissent qu'une fois que la fixation du mutant précédent est réalisée (Geritz et al. 1998).

Parce que la fonction de *minimum* est discontinue, il faut établir les combinaisons de caractères  $(y,z)$  telles que la fin de la période reproductive est indépendante du cancer, et celles telles que les lésions cancéreuses interrompent prématurément la période reproductive.

$$T_{critical} \geq T_{old} \leftrightarrow \frac{-y + z \text{Log} \left[ \frac{C_{critical}}{A} \right]}{\alpha + \beta \text{Log} \left[ \frac{C_{critical}}{A} \right]} \geq T_{old} \quad (3)$$

$$\leftrightarrow y \leq -\alpha T_{old} + (z - \beta T_{old}) \text{Log} \left[ \frac{C_{critical}}{A} \right] \quad (4)$$

$$\leftrightarrow z \geq \beta T_{old} + \frac{\alpha T_{old} + y}{\text{Log} \left[ \frac{C_{critical}}{A} \right]} \quad (5)$$

Les combinaisons de caractères  $(y,z)$  qui autorisent leurs porteurs à se reproduire jusqu'à la fin de leur période reproductive doivent donc respecter les conditions 4 et 5 ; une application numérique est présentée dans la figure 2. Pour les espèces dont la période reproductive est très courte ( $T_{old} \rightarrow 0$ ), les conditions 4 et 5 se résument à  $C_{critical} \leq A e^{\frac{y}{z}}$  : c'est à dire que pour se reproduire, les individus doivent ne pas avoir de cancer à leur naissance. Au contraire, pour les populations dont la période reproductive est très longue ( $T_{old} \rightarrow +\infty$ ), les conditions 4 et 5 reviennent à  $y \rightarrow -\infty$  et  $z \rightarrow +\infty$  : c'est à dire que, du fait de l'accumulation irréversible de mutations pro-cancéreuses, il est impossible pour un individu d'aller jusqu'au bout de sa période reproductive sans être touché par un cancer.

Aussi, à la condition  $T_{critical} \geq T_{old}$ , la période reproductive se termine avant que les cancers aient un impact clinique, de sorte qu'on a  $W(y, z) = w T_{old}$  et :

$$\frac{\partial}{\partial y} W [y, z] = \frac{\partial}{\partial z} W [y, z] = 0$$

La valeur sélective des individus ne varie donc pas, pourvu que les combinaisons de caractères  $(y, z)$  remplissent les conditions 4 et 5. Il n'y a alors pas de sélection sur ces combinaisons de caractères, qui se trouvent à l'équilibre neutre.

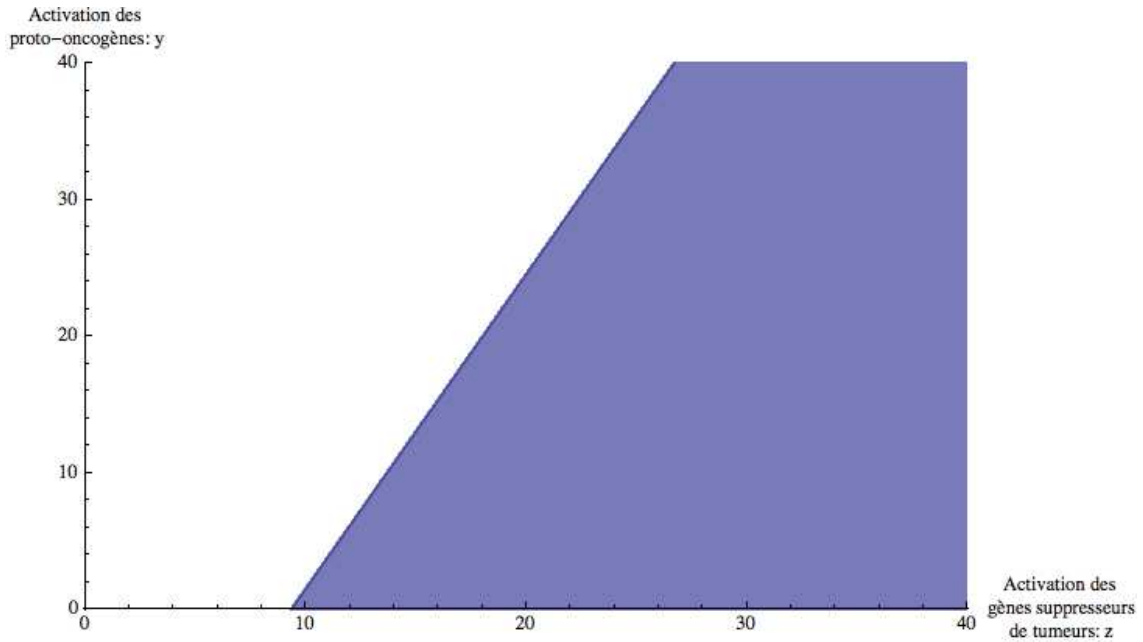


Figure 2 – Les combinaisons de caractères  $(y, z)$  qui remplissent les conditions 4 et 5 sont représentées en bleu. Les valeurs de caractères  $y$  et  $z$  sont considérées en unités arbitraires. Les valeurs de paramètres suivantes ont été utilisées :  $w = 1$ ,  $\alpha = 2$ ,  $\beta = 1$ ,  $A = 1$ ,  $C_{critical} = 10$ ,  $T_{old} = 5$

Pour les combinaisons de caractères  $(y, z)$  qui ne remplissent pas ces conditions, les organismes souffrent de cancer durant leur période reproductive. Leur valeur sélective revient donc à :

$$W [y, z] = w \frac{-y + z \text{Log} \left[ \frac{C_{critical}}{A} \right]}{\alpha + \beta \text{Log} \left[ \frac{C_{critical}}{A} \right]}$$

D'où :

$$\frac{\partial}{\partial y} W [y, z] = \frac{-w}{\alpha + \beta \text{Log} \left[ \frac{C_{critical}}{A} \right]}$$

$$\frac{\partial}{\partial z} W [y, z] = \frac{w \text{Log} \left[ \frac{C_{critical}}{A} \right]}{\alpha + \beta \text{Log} \left[ \frac{C_{critical}}{A} \right]}$$

Nous supposons que l'activation des gènes proto-oncogènes doit surpasser celle des gènes suppresseurs de tumeur pour que les lésions atteignent le stade critique : pour des valeurs positives de  $y$  et  $z$ , cela revient à ne considérer que les cas tels que  $A \leq C_{critical}$ . Aussi, dans ces cas, on peut trouver  $\frac{\partial}{\partial y}W[y,z] \leq 0$  et  $\frac{\partial}{\partial z}W[y,z] \geq 0$ . Par conséquent, les niveaux d'activation initiaux sont sous sélection négative pour les proto-oncogènes  $y$ , et sous sélection positive pour les gènes suppresseurs de tumeur  $z$ .

Ainsi, une valeur positive de  $y$  peut envahir la population résidente, si et seulement si elle remplit les conditions 4 et 5, c'est à dire que les défenses anti-cancer sont suffisamment élevées pour compenser le processus oncogénique jusqu'à la fin de la période reproductive. Des diagrammes d'invasibilité sont présentés dans la figure 3 pour différentes valeurs de  $z$ . Pour  $z = 0$ , aucune valeur de  $y$  ne peut envahir la population : un individu ne peut donc pas vivre ni se reproduire en l'absence de défenses anti-cancer. Pour  $z = 5$ , on observe qu'aucune mutation positive sur  $y$  ne peut envahir la population, avec un équilibre évolutionnaire à  $y^* = 0$  : la présence de défenses anti-cancer ne suffit pas à elle seule à autoriser la persistance d'allèles à effet pro-oncogénique. Il faut que ces défenses soient suffisamment exprimées chez l'individu : au dessus d'un seuil de défense anti-cancer, pour  $z = 15$ , on observe un espace d'équilibre neutre où toutes les mutations (positives ou négatives) sur  $y$  peuvent envahir la population. Cet équilibre neutre est borné par la condition 5, au dessus de laquelle l'invasion est impossible. Pour des valeurs plus fortes de  $z$  (p. ex.  $z = 25$ ), on notera que plus les défenses anti-cancer sont élevées, et plus la borne autorisant l'invasion est élevée.

**Conclusion** Les allèles pro-oncogéniques sont néfastes aux organismes, à tout moment de leur vie. S'ils favorisent l'apparition d'un cancer avant la fin de la période reproductive, alors ils défavorisent la reproduction de leurs porteurs, et défavorisent par conséquent leur propre transmission dans les populations. Néanmoins, si leur effet oncogénique est compensé jusqu'à la fin de la période reproductive, alors ces gènes n'ont aucun effet sur la valeur sélective de l'individu, et peuvent donc se transmettre à la descendance de la même manière que n'importe quel allèle neutre. Les gènes suppresseurs de tumeur ralentissent la progression des lésions cancéreuses, mais sont progressivement inactivés par les mutations somatiques : ainsi, plus ils sont nombreux et activés à la naissance, et plus le risque de cancer précoce est faible pour l'organisme (Abegglen et al. 2015).

Un allèle pro-cancéreux peut donc être hérité et transmis à la descendance dans des espèces possédant une période post-reproductive et des mécanismes (tels que les gènes suppresseurs de tumeur) capables de compenser l'effet de ces allèles jusqu'à cette période post-reproductive.

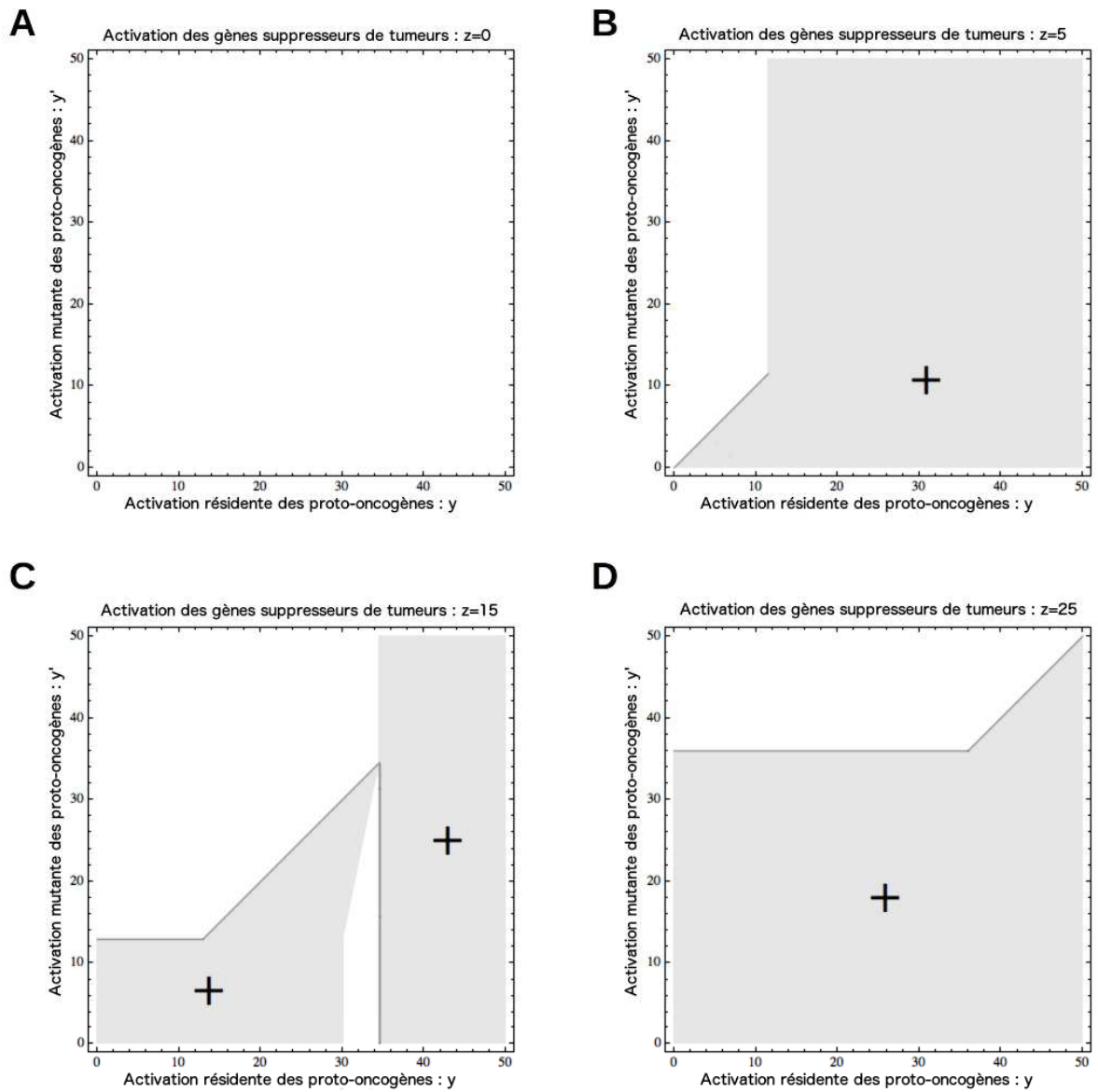


Figure 3 – Diagramme d’invasion pour l’activation des proto-oncogènes  $y$ , pour une activation des gènes suppresseurs de tumeur (A)  $z = 0$ , (B)  $z = 5$ , (C)  $z = 15$ , et (D)  $z = 25$ . Les valeurs de caractères  $y$  et  $z$  sont considérées en unités arbitraires. Les valeurs de paramètres suivantes ont été utilisées :  $w = 1$ ,  $\alpha = 2$ ,  $\beta = 1$ ,  $A = 1$ ,  $C_{critical} = 10$ ,  $T_{old} = 5$

## Partie IV

# Des tumeurs aux populations

Les interactions biologiques constituent une des contraintes principales sur l'évolution des organismes. En particulier, les interactions antagonistes entre hôtes et parasites favorisent l'évolution de nombreux caractères chez les deux partenaires. Au cours des générations, les parasites tendent à sélectionner toute adaptation permettant de faciliter leurs interactions avec leurs hôtes : pour les rencontrer, les pénétrer ou s'y accrocher, consommer leurs ressources, survivre à l'hôte et s'y reproduire, puis se transmettre vers de nouveaux hôtes. Au contraire, les hôtes tendent à sélectionner toute adaptation leur permettant de réduire l'impact du parasite sur leur survie et leur fécondité : en évitant les rencontres et les contacts de parasites, en résistant aux parasites pour les éliminer, ou en tolérant ses impacts pour minimiser les pertes. Ces adaptations et contre-adaptations s'influencent mutuellement, et peuvent atteindre une complexité particulièrement élevée : en témoignent la capacité de nombreux parasites à modifier la physiologie et le comportement de leurs hôtes (manipulation), et les systèmes immunitaires complexes de nombreux taxons d'hôtes.

Le cas des cellules cancéreuses est complètement à part : elles dérivent des organismes qu'elles parasitent, et ne persistent généralement pas au delà de la mort de l'individu. Pour autant, l'interaction entre les organismes et leurs cellules cancéreuses peut aussi être qualifiée d'antagoniste. On peut donc s'attendre à ce que les cellules cancéreuses et les organismes développent également des adaptations et des contre-adaptations : pour faciliter l'interaction pour les unes, pour la combattre pour les autres.

Ce chapitre abordera donc l'interaction des populations de cellules cancéreuses avec les populations d'organismes, et l'influence réciproque que ces deux partenaires entretiennent au cours de l'évolution des organismes. Dans un premier temps, j'expose un modèle d'évolution emboîtée pour évaluer l'impact de différentes conditions écologiques sur l'évolution des défenses au cancer, et notamment tester dans quelles conditions la sélection naturelle favorise la tolérance davantage que la résistance au cancer (section 9). Dans un second temps, je propose une perspective sur l'impact de l'évolution des cellules cancéreuses sur le phénotype des organismes, en postulant notamment que de nombreuses modifications phénotypiques sont imputables à une manipulation de la part des cellules cancéreuses (section 10).



## 9 Evolution emboîtée des mécanismes de défenses contre le cancer

**Titre :** *The Evolution of Resistance and Tolerance to Cancer*

**Auteurs :** Tazio Tissot<sup>11</sup>, Frédéric Thomas<sup>12</sup>, Beata Ujvari, Benjamin Roche<sup>12</sup>

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1 **The evolution of resistance and tolerance to cancer.**

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11 **Keywords:** cancer; resistance; tolerance; nested model; evolution

12

13 **Abstract**

14 Organisms may respond to fitness threatening external or internal hazards by either fighting the  
15 threat or by mitigating its impact on fitness. The evolution of these two defense mechanisms,  
16 resistance and tolerance, has been widely studied in host-parasite interactions, but has never been  
17 addressed in cancer. Similar to their parasitic counterparts, defenses against cancer may evolve  
18 during the organism's lifetime. However, cancer evolution stops at the organism's death, and  
19 therefore acts as a constant pressure on the organisms' health. In this study, we use a nested  
20 approach to investigate how resistance and tolerance strategies to cancer are selected at various  
21 scales: within organisms, between organisms, and both at the same time. We find that, within  
22 organisms, natural selection favors healthy cells tolerant to cancer, as they persist much longer  
23 under cancer threat. When selection operates at an inter-individual scale, tolerant organisms are  
24 favored in most ecological contexts, but resistance is a better strategy for late-breeding organisms  
25 living under high cancer threat. Finally, natural selection favors more resistance for the organism  
26 when defenses can evolve during life compared to when they cannot. This contrasted pattern of

27 selection between organisms and their cells may testify of a conflict between these two units of  
28 selection, since resistance favors organismal fitness over cellular fitness.

## 29 **1. Introduction**

30 When organisms cannot avoid a potential threat to their fitness, they can adopt two different  
31 strategies to reduce its burden. Resistance aims at diminishing/suppressing the threat, whereas  
32 tolerance rather alleviates its impact on the organism's fitness (Nuñez-Farfan et al. 2007; Råberg et  
33 al. 2009; Svensson and Råberg 2010; Levin-Reisman et al. 2017). The evolution of these strategies  
34 has been extensively studied in host-parasite interactions (Råberg et al. 2009). Resistance minimizes  
35 the success of a parasite by preventing its establishment or inhibiting its growth (*i.e.*, parasite  
36 burden). By contrast, a tolerant host, although susceptible, acts to minimize the fitness effects of  
37 infection, without directly affecting parasite fitness. In these cases, resistance and tolerance are not  
38 mutually exclusive (Restif and Koella 2004), but their co-occurrence in a single individual is  
39 usually limited by tradeoffs (Råberg et al. 2009; Lefèvre et al. 2010, 2011) and distinct evolution  
40 (Miller et al. 2005).

41 As cancer poses a threat to organisms (Vittecoq et al. 2013), they deploy similar defense strategies  
42 to deal with this fitness reducing internal factor (Goldszmid et al. 2014; Dillman and Schneider  
43 2015; van Niekerk et al. 2016). Indeed, there are several cancer suppression mechanisms, from cell-  
44 intrinsic checks that prevent uncontrolled cell proliferation and invasion of other tissues and organs  
45 (*e.g.*, apoptosis, effective DNA repair, epigenetic modifications, cell cycle checkpoints, telomere  
46 shortening), to integral controls that suppress cancer by operating at the level of tissue organization  
47 (*e.g.*, tissue architecture, and immune surveillance, DeGregori 2011; Harris et al. 2017). Else,  
48 potential mechanisms for tolerance strategies have not been accurately identified so far. Yet, an  
49 organism's health decay does not always correlates with the load of cancer cells, which suggests  
50 that such strategies of defense against cancer could actually exist (Dillman and Schneider 2015).  
51 For example, repairing cancer wounds might be involved in the increased survival of tolerant  
52 organisms (Vaidya et al. 2003; Zarchi et al. 2015).

53 Because malignant cells and microparasites display a lot of similarities in the way they progress and  
54 evolve within their hosts (Dingli and Nowak 2007; Duesberg et al. 2011), it is expected that, in

55 addition to resistance mechanisms, selection should have favored forms of tolerance to malignant  
56 progression. A major difference, however, between malignant cells and microparasites, is the lack of  
57 between host transmission for the former (but see Ujvari et al. 2016b), preventing antagonistic  
58 coevolution to occur over evolutionary time between hosts and malignant cells. Thus, while host  
59 traits that alleviate the burden of cancer during one generation can be passed on across generations,  
60 cancer adaptations to circumvent malignant formation and progression (conversely to the  
61 adaptations of microparasites) systematically disappear when tumor bearing individuals die (Arnal  
62 et al. 2015).

63 The evolution of defense mechanisms to cancer is highly complex, and hence trying to deciphering  
64 it requires a multilayer, nested approach. Indeed, the evolution of organisms depends on how cancer  
65 progression affects their fitness. Conversely, the progression of malignant cells depends on how  
66 resistance and tolerance influence their evolution within the organism. Both the evolution of  
67 organisms in their environments and the evolution of cancer cells in their microenvironments  
68 should be linked to understand which defense strategy would best fit the organism and would likely  
69 be favored by natural selection.

70 Here, we investigate how intra- and inter-organism eco-evolutionary dynamics impact the evolution  
71 of resistance and tolerance to cancer through a nested approach. On the one hand, we model the  
72 eco-evolutionary dynamics of healthy cells alongside several cancer cell types, in order to  
73 determine how these traits impact phenotypic changes in the populations (*i.e.*, intra-organism  
74 evolution) of healthy and malignant cells. On the other hand, we link cancer progression to the  
75 organism's fitness, which allows us to identify in which species and environments resistance and  
76 tolerance should be favored by natural selection.

77

## 78 **2. Materials and methods**

79 Cancer-organism interactions are usually explored within the organism (see *e.g.*, Basanta et al.  
80 2012; Pacheco et al. 2014), despite the intra-organism processes may impact organisms' survival

81 and fertility. Here, we nest intra-organism dynamics into an inter-organism model to address the  
 82 evolution of organisms' defenses against cancer according to the strategies heritability.

83

## 84 **2.1 General intra-organism dynamics**

85 We aim to track the eco-evolutionary dynamics occurring within and between organisms. To do so,  
 86 we consider a system of differential equations describing the temporal dynamics of cell densities  
 87 within an organism:

88

$$\begin{cases} \frac{dH}{dt} = (1 - \gamma) \left( b + \beta \left( 1 - \frac{H}{H_0} \right) \right) H X - \mu H - \kappa_H H (C_S + C_{NS}) \\ \frac{dX}{dt} = -\iota X \left( b + \beta \left( 1 - \frac{H}{H_0} \right) \right) H \\ \frac{dC_S}{dt} = (1 - \sigma) (b + s) C_S - \mu C_S - \kappa_S C_S (C_{NS} + I) + \gamma \left( b + \beta \left( 1 - \frac{H}{H_0} \right) \right) H X \\ \frac{dC_{NS}}{dt} = (b + s) C_{NS} - \mu C_{NS} - \kappa_{NS} C_{NS} C_S + \sigma (b + s) C_S \\ \frac{dI}{dt} = \alpha C_S I \end{cases} \quad (1)$$

89 These equations allow tracking the densities of four cell types: healthy cells  $H$ , sensitive cancer  
 90 cells  $C_S$ , insensitive cancer cells  $C_{NS}$ , and immune cells  $I$ . Healthy and cancer cells divide and die  
 91 at basal division and mortality rates  $b$  and  $\mu$ . However, cancer cells also have a competitive  
 92 advantage in proliferation  $s$ , and the healthy cell pool recovers from supplementary death at rate  $\beta$ .  
 93 In order to take into account the slowdown in division due to telomere shortening (see *e.g.*, Herbert  
 94 et al. 1999), healthy cells' division rate is weighted by a factor  $X(t)$  decreasing with divisions:

95

$$\frac{dX}{dt} = -\iota X b H$$

96 where  $\iota$  is the rate of telomere decay. Across divisions, healthy cells have a probability  $\gamma$  to mutate  
 97 and turn into sensitive cancer cells  $C_S$ . Sensitive cancer cells have themselves a probability  $\sigma$  to  
 98 mutate and turn into insensitive cancer cells  $C_{NS}$  across divisions.

99 Since cancer negatively impacts the organism's health, we consider cancer cells to negatively  
 100 interfere with healthy cells according to their respective densities and to an interference rate  $\kappa_H$ .  
 101 Moreover, competition is a widespread interaction between cancer subclones, and sensitive and

102 insensitive cells negatively interfere with each other according to their respective densities and  
103 respective competition rates  $\kappa_S$  and  $\kappa_{NS}$ .

104 In order to track the effects of the organism's defenses on cancer progression, we introduce two  
105 traits of resistance and tolerance in the system of equations (1).

106 Healthy cells can tolerate the negative interference of cancer, by mitigating the density decrease and  
107 thus recovering. We thus consider the tolerance strategy for healthy cells as a raise of division rate

108 when healthy cells' density decreases:  $\beta \left(1 - \frac{H}{H_0}\right)$ , where  $H_0$  the initial density of healthy cells,  
109 and  $\beta$  the investment in tolerance. It is to note that, in the absence of cancer, healthy cells should  
110 divide as often as they die: *i.e.*,  $b = \mu$ .

111 As well as healthy cells might tolerate cancer, they also might resist and reduce the cancer load.  
112 Immune cells  $I$  are a fourth player in the general intra-organism dynamics, to model the anti-tumor  
113 immunity. As used in previous models of resistance to parasites (André et al. 2003; André and  
114 Gandon 2006), we consider immune cells to divide through exponential dynamics as soon as they  
115 detect cancer cells, according to a division rate  $\alpha$  describing the investment in resistance. Immune  
116 cells impede cancer growth, but have also been shown to select for the cancer subclones able to  
117 escape resistance (Khong and Restifo 2002). Thus, we consider immune cells to only interfere with  
118 sensitive cancer cells (which parameter  $\kappa_S$  also describes), but not with insensitive cancer cells.

119 Finally, we consider resistance and tolerance to be linked by a concave tradeoff:

120

$$\frac{\alpha}{\alpha_0} = 1 - \sqrt{1 - \left(1 - \frac{\beta}{\beta_0}\right)} \quad (2)$$

121 where  $\alpha_0$  and  $\beta_0$  are ad-hoc coefficients to link resistance and tolerance strategies. Indeed, tissue  
122 repair involves several pathways of innate immunity (Gurtner et al. 2008; Wynn and Vannella  
123 2016), which oppose anti-tumor immunity (Meyer et al. 2011; Ostuni et al. 2015).

124

125

126 **2.2 Intra-organism evolution**

127 In order to model the evolution of defense strategies within an organism, we modify the system (1)

128 to include the eco-evolutionary dynamics of healthy cells:

129

$$\left\{ \begin{array}{l} \frac{dH_i}{dt} = (1 - \gamma) \left( b + \beta_i \left( 1 - \frac{\sum_i H_i}{H_0} \right) \right) H_i X_i - \mu H_i - \kappa_H H_i (C_S + C_E) \\ \quad - 2\zeta H_i + \zeta (H_{i-1} + H_{i+1}) \\ \frac{dC_S}{dt} = (1 - \sigma) (b + s) C_S - \mu C_S - \kappa_S C_S (C_E + I) + \gamma \sum_i \left( b + \beta_i \left( 1 - \frac{\sum_i H_i}{H_0} \right) \right) H_i X_i \\ \frac{dC_E}{dt} = (b + s) C_E - \mu C_E - \kappa_E C_E C_S + \sigma (b + s) C_S \\ \frac{dI}{dt} = \bar{\alpha} C_S I \\ \frac{dX_i}{dt} = -\iota X_i \sum_i \left( b + \beta_i \left( 1 - \frac{\sum_i H_i}{H_0} \right) \right) H_i \\ \quad + \left( \frac{H_i X_i + \zeta (H_{i-1} X_{i-1} + H_{i+1} X_{i+1} - 2 H_i X_i)}{H_i + \zeta (H_{i-1} + H_{i+1} - 2 H_i)} - X_i \right) \end{array} \right.$$

130

(3)

131 with  $\bar{\alpha} = \frac{1}{\sum_i H_i} \sum_i \alpha_i H_i$  being the mean resistance strategy. In these equations, we consider the

132 healthy cells of an organ to be able to shift strategies over a vector of resistance and tolerance

133 strategies. Indeed, phenotypic plasticity allows healthy cells to shift from phenotype to another

134 (Bjornson et al. 1999; Wagers and Weissman 2004), *i.e.*, mutations are not necessary for strategy

135 shifts. Thus, all the healthy cells of an organ might not share the same strategies of resistance and

136 tolerance against cancer, as they would change over the organism's lifetime. The density of healthy

137 cells behaving according to strategies  $(\alpha_i, \beta_i)$  is denoted  $H_i$ , and their telomere shortening rates  $X_i$ .

138 Healthy cells  $H_i$  can shift from their strategies  $(\alpha_i, \beta_i)$  to the neighboring strategies  $(\alpha_{i-1}, \beta_{i-1})$

139 and  $(\alpha_{i+1}, \beta_{i+1})$ , according to the shift rate  $\zeta$ . Telomere shortening rates are adjusted as cells are

140 added or subtracted to each population. These equations allow tracking the instantaneous

141 frequencies of resistance and tolerance strategies within a population of healthy cells confronted to

142 emergence of cancer cells.

143



144 **2.3 Inter-organism model**

145 Considering the general within-individual dynamics described previously, cancer will impact the  
 146 density of healthy cells able to fulfill the physiological needs of the organism. Because cancer  
 147 lowers the organism's fitness, the defenses against cancer may be naturally selected in populations.  
 148 To take into account such a process, we model the impacts of cancer on organisms' reproduction  
 149 rate, when healthy cells do not evolve.

150 We assume that resistance ( $\alpha$ ) and tolerance ( $\beta$ ) to cancer are genetically encoded traits, and we  
 151 consider their evolution in a population of organisms whose average lifespan is  $L$ . According to  
 152 Euler-Lotka equation (Lotka 1922), the reproduction rate  $P_i$  of any individual following strategy  
 153  $(\alpha_i, \beta_i)$  can be computed as:

154

$$P_i = \int_0^L \lambda_i(t) \phi_i(t) dt \quad (4)$$

155 where  $\lambda_i(t)$  and  $\phi_i(t)$  are respectively the probability to be alive and the mean fertility rate at time  $t$ .  
 156 In order to track how life-history traits influence the evolution of resistance and tolerance strategies,

157 we consider that the species is only fertile during half of its life (i.e., during  $\frac{L}{2}$ ). Its reproductive  
 158 period starts at age  $t_{min}$  and lasts until age  $t_{min} + \frac{L}{2}$ . We assume that tissue repair and immunity

159 are costly, which yields a tradeoff between resistance, tolerance and fertility such as:

160

$$\phi_i(t) = \begin{cases} \frac{\phi_0}{1 + \frac{1}{2} (\alpha_i/\alpha_0 + \beta_i/\beta_0)} & \text{if } t \geq t_{min} \text{ and } t < t_{min} + \frac{L}{2} \\ 0 & \text{if } t < t_{min} \text{ or } t \geq t_{min} + \frac{L}{2} \end{cases} \quad (5)$$

161 Cancer itself is known to reduce organisms' survival. Yet, how it precisely impacts survival across  
 162 reproductive life remains unknown (Vittecoq et al. 2013). We assume that the probability to be alive  
 163 at time  $t$  is:

164

$$\frac{d\lambda_i}{dt} = -\lambda_i \left( \omega_1 \frac{H_0 - H}{H_0} + \omega_2 \frac{C_S + C_{NS}}{H + C_S + C_{NS}} \right) \quad (6)$$

165 where  $\omega_1$  and  $\omega_2$  are coefficients depending on the organ's size and relevance to survival (as  
 166 suggested in Thomas et al. 2016). Survival was thus considered as decreasing with the load of  
 167 cancer cells (André et al. 2003; André and Gandon 2006; Gilchrist and Coombs 2006), but also with  
 168 the loss of healthy cells (Antia et al. 1994; van Baalen and Beekman 2006), as previously suggested  
 169 in models of host-parasite evolution. We assume cancer development to interact with no other trait  
 170 in the organism's phenotype. Thus, we include this measure of reproduction in population-scale  
 171 dynamics:

172

$$\begin{aligned} \frac{dN_i}{dt} = & P_i N_i \left(1 - \frac{\sum_i N_i}{K}\right) (1 - 2\tau) - \delta N_i \\ & + \tau \left(1 - \frac{\sum_i N_i}{K}\right) (N_{i-1} P_{i-1} + N_{i+1} P_{i+1}) \end{aligned} \quad (7)$$

173 Each genotype  $N_i$  following a given strategy  $(\alpha_i, \beta_i)$  give birth at a rate  $P_i$ . We characterize  
 174 intrapopulation competition by using a logistic function with carrying capacity  $K$  (Sibly et al. 2005).  
 175 Newborn organisms have a probability  $\tau$  to turn into a neighboring genotype  $(\alpha_{i-1}, \beta_{i-1})$  or  
 176  $(\alpha_{i+1}, \beta_{i+1})$  by mutation. Mortality rate  $\delta$  does not differ from one genotype to another.

177

## 178 **2.4 Nested model**

179 We previously considered distinct intra-organism and inter-organism evolution of defenses against  
 180 cancer. These models allow to track the evolution of resistance and tolerance to cancer respectively:

181 (i) among healthy cell populations during an organism's lifetime, and (ii) among organism  
 182 populations over several generations. Both processes can actually occur together: any organism can  
 183 inherit an initial strategy  $(\alpha_i, \beta_i)$ , which will evolve during its lifetime. We therefore explore the  
 184 evolution of resistance and tolerance against cancer by nesting the intra-organism model into the  
 185 inter-organism one.

186 Being assumed that every healthy cell of an organ share the same genotype, we consider that only  
 187 one pair of strategies  $(\alpha_i, \beta_i)$  is initially present in a population of healthy cells. No strategies but  
 188 the initial ones are genetically encoded in the organism's genome and passed on to the offspring. In

189 order to study the evolution of the initial resistance and tolerance strategies, we integrate the  
 190 equations of system (4) in an inter-organism model, following the same assumptions than above.  
 191 Thus, we adapt equation (6) to compute the survival rate:

$$192 \quad \frac{d\lambda_i}{dt} = -\lambda_i \left( \omega_1 \frac{H_0 - \sum_k H_k}{H_0} + \omega_2 \frac{C_S + C_{NS}}{\sum_k H_k + C_S + C_{NS}} \right) \quad (8)$$

193 and the mean fertility rate in the same manner as equation (6):

$$194 \quad \phi_i(t) = \begin{cases} \frac{1}{1 + \frac{1}{2} \sum_k (\alpha_k/\alpha_0 + \beta_k/\beta_0) \zeta^{|k-i|}} & \text{if } t \geq t_{min} \text{ and } t < t_{min} + \frac{L}{2} \\ 0 & \text{if } t < t_{min} \text{ or } t \geq t_{min} + \frac{L}{2} \end{cases} \quad (9)$$

195 with  $(\alpha_i, \beta_i)$  being the initial pair of strategies. We consider populations of organisms to follow the  
 196 same dynamics previously described in equation (7).

197

## 198 **2.5 Numerical simulations**

199 We consider here thirty different combinations of  $\alpha$  and  $\beta$ , ranging from (0, 1) to (1, 0). We  
 200 employed numerical simulations to compute the outcome of intra- and inter-organism evolution of  
 201 these strategies. Evolution in healthy cell populations is limited to the lifetime of the organism. Thus  
 202 we could not expect any strategy to become fixed within an organism. We therefore analyzed the  
 203 most frequent strategies at the end of an organism's lifetime (*i.e.*, the *dominant* strategies) to be  
 204 favored by natural selection.

205 On the contrary, organisms evolve over infinite time, which allows a strategy to become fixed in a  
 206 population. Then, to analyze the inter-organism and the nested models, we assumed individuals to  
 207 inherit resistance and tolerance strategies, and not to differ in any other phenotypic trait at any scale.  
 208 They reproduce according to their reproduction rate  $P(\alpha, \beta)$ , unless the total population has  
 209 reached the carrying capacity. Thus, provided that mutations allow individuals to shift these initial  
 210 strategies, natural selection should result in a raise in frequency of the fittest genotypes. The  
 211 beginning of the reproductive period  $t_{min}$  is considered as intrinsic to the species, and the  
 212 probability for a healthy cell to become cancerous  $\gamma$  as the extrinsic cancer exposure. We thus

213 employed numerical simulations to compute the fitness of each strategy, and then to determine the  
214 outcome of population dynamics after enough time for a strategy to become fixed (here, after 400  
215 generations).

216 The intra- and inter-organism model were simulated on cancer exposures ( $\gamma$ ) ranging from  $10^{-5}$  to  
217  $10^{-2}$  and on reproductive periods which started at ages ranging from 1 to  $\frac{L}{2} + 1$ . The other parameter  
218 values are described in Table 1.

219

220

221 **Table 1: Parameter values of the model**

Parameter	Meaning	Value
$H_0$	Initial density of healthy cells	1
$X_0$	Initial telomere length	1
$C_{S0} = C_{NS0}$	Initial density of sensitive and insensitive cancer cells	0
$\lambda_0$	Initial probability to survive	1
$I_0$	Initial density of immune cells	$10^{-2}$
$b = \mu$	Basal division and death rates per unit of time	1
$s$	Selective advantage on cancer cells' division rates	0.1
$\iota$	Telomere shortening rate per unit of time	$10^{-4}$
$\omega_1 = \omega_2$	Survival decay rates	$5 \cdot 10^{-2}$
$\kappa_H = \kappa_S = \kappa_{NS}$	Interference rates for healthy, sensitive and insensitive cells	$10^{-2}$
$\zeta$	Strategy shift rate per unit of time in cell populations	0.24
$\tau$	Strategy shift rate per unit of time in organism populations	$2 \cdot 10^{-3}$
$\gamma$	Healthy to cancer cell mutation rate per division	$[10^{-5} - 10^{-2}]$
$\sigma$	Sensitive to insensitive cell mutation rate per division	$10^{-4}$
$\phi_0$	Maximal fertility rate per unit of time	1
$L$	Average lifespan of an organism	70
$t_{min}$	Age of reproductive maturity	$[1 - L/2]$
$\alpha_0$	Investment coefficient in resistance to cancer	1
$\beta_0$	Investment coefficient in tolerance to cancer	1
$\delta$	Mortality rate in populations	$\frac{1}{2} \max_i(P_i)$
$K$	Carrying capacity of organism populations	1
$N_{i0}$	Initial density of each strategy in an organism population	$K/30$

222

223

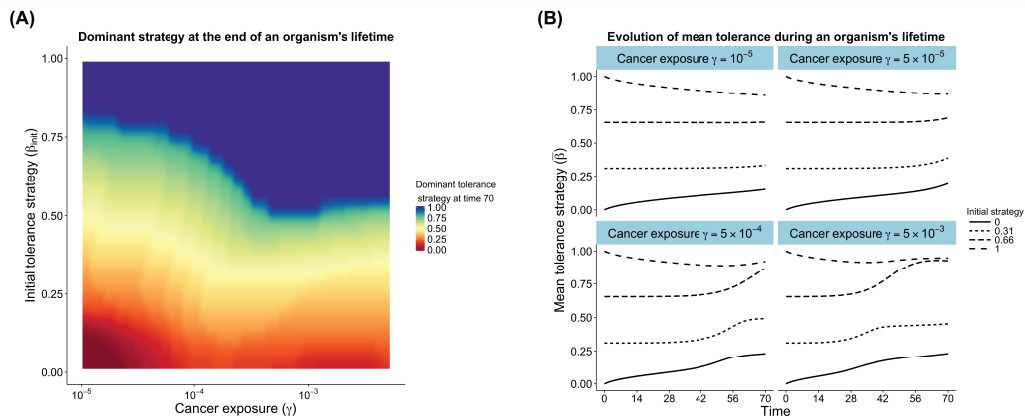
224

225 **3. Results**

226 **3.1 Intra-organism evolution of resistance and tolerance to cancer**

227 We first investigated how different defense strategies would help healthy cells to survive and divide  
 228 under the burden of carcinogenesis and would evolve during an organism's lifetime. Healthy cells  
 229 could either fight cancer cells (resistance), or grow faster to outcompete them (tolerance), or a  
 230 mixture of both. Dominant and average strategies were tracked across time in the pool of healthy  
 231 cells, for gradients of initial strategies and cancer exposures.

232 We found that, when cancer exposure is low, final dominant strategies are phenotypically close to  
 233 the initial strategies. When cancer exposure is high, the most tolerant strategies end up dominating  
 234 the population for most initial cases (Fig. 1A). Despite the most tolerant strategies rarely have  
 235 enough time to dominate the healthy cell pool, the population always evolves towards high levels of  
 236 tolerance for high cancer exposure (always higher than  $\beta = 2/3$  in this case, Fig. 1B). Accordingly,  
 237 the final strategy is more tolerant when cancer exposure is high, and the most tolerant strategies  
 238 invade more quickly in this case.



239  
 240 **Figure 1: Influence of initial strategy and cancer exposure on within-host evolution of resistance and**  
 241 **tolerance to cancer.** (A) Dominant tolerance strategy at the end of an organism's lifetime. The initial strategy is the tolerance strategy initially  
 242 introduced in the population. The dominant strategy is the most frequent strategy in the population at a given time, and is considered as favored by  
 243 natural selection. The continuum of naturally selected strategies between full tolerance and full resistance is depicted in shades from red to violet: the  
 244 reddest shades account for resistant strategies, while the most violet shades represent tolerant strategies. (B) Mean tolerance strategies over time: the  
 245 evolution of mean tolerance strategy over time is displayed for initial strategies  $\beta_{init}$  in [0, 0.31, 0.66, 1]. Parameters used are reported in Tab. 1.

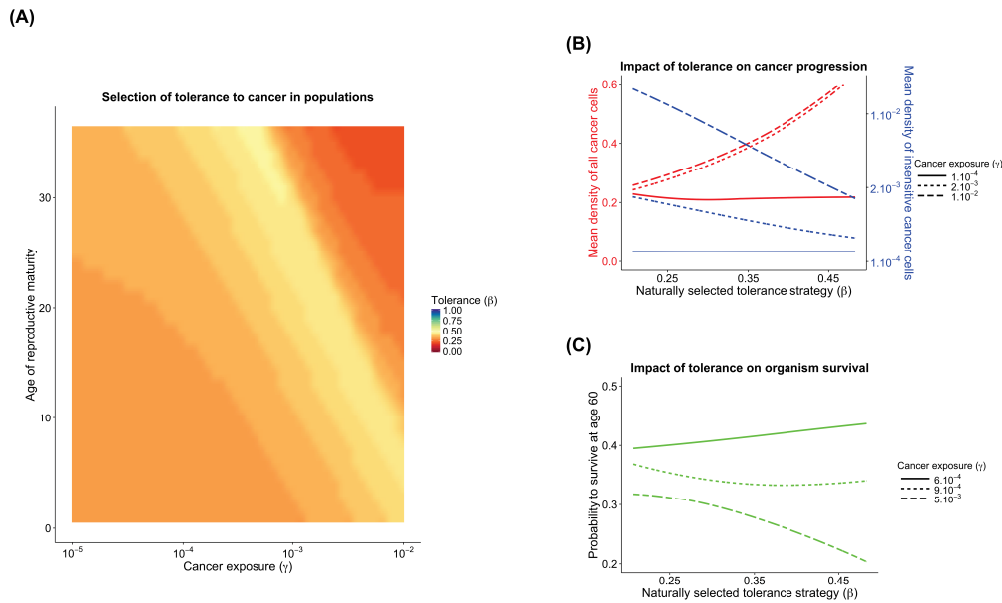
246 **3.2 Inter-organism evolution of resistance and tolerance to cancer**

247 We analyzed how evolution may select inheritable mechanisms that decrease the burden of cancer  
248 in a species, depending on intrinsic (the age of reproductive maturity) and extrinsic factors (cancer  
249 exposure). Strategies were investigated along a gradient between a full investment in decreasing the  
250 load of cancer cells and a full investment in decreasing their impacts on organisms' survival.

251 We found that intrinsic and extrinsic factors interact in contrasting ways with the selection for  
252 resistance and tolerance to cancer (Fig. 2A). For early-reproducing organisms that are little exposed  
253 to cancer, natural selection favors an intermediate level of tolerance in cancer defense strategies.  
254 Then, selected tolerance increases both with cancer exposure and with the age of maturity, when at  
255 least one of them is low. For late-reproducing organisms that are highly exposed to cancer, natural  
256 selection rather favors individuals that are highly resistant to cancer. The selection for tolerance is  
257 actually strongest for late-reproducing individuals that are exposed to medium levels of cancer risk.

258 To understand this pattern, we investigated how resistance and tolerance impact cancer progression.  
259 Organisms have to deal with larger densities of cancer cells (*i.e.*, larger tumors) when cancer  
260 exposure is high. Yet, regardless of extrinsic cancer exposure, organisms that tolerate cancer  
261 actually form larger tumors than those who resist to cancer (Fig. 2B). Tumors of tolerant organisms  
262 contain a higher diversity of cell types than those of resistant organisms: tolerance, conversely to  
263 resistance, does not select for any particular cell type within a tumor. These particularities of each  
264 strategy are associated with diverse impacts on survival (Fig. 2C). Tolerance is associated with  
265 increased survival at low cancer exposures, but with reduced survival at high cancer exposures.

266



267

268 **Figure 2: Influence of the age of reproductive maturity and cancer exposure on organism evolution of**

269 **resistance and tolerance to cancer.** (A) Naturally selected tolerance strategies for ranges of life history traits and cancer exposure. The

270 continuum of naturally selected strategies between full tolerance and full resistance is depicted in shades from red to violet: the reddest shades

271 account for resistant strategies, while the most violet shades represent tolerant strategies. (B) Impact of tolerance on organism survival. Various cancer

272 exposures are depicted in full or dotted lines. (C) Impact of tolerance on cancer progression. Mean density of all cancer cells (sensitive and escaping

273 cells) over an organism's lifetime is displayed in red, and mean density of insensitive cancer cells over an organism's lifetime in blue. Parameters used

274 are reported in Tab. 1.

275

### 276 3.3 Nested intra- and inter-organism evolution of resistance and tolerance to cancer

277 Above, we investigated how natural selection could balance between two defense strategies against

278 cancer, at several levels, through their effects on both cell and organism fitness. Tolerance to cancer

279 is favored in healthy cell populations, whereas resistance can be selected in late-breeding organisms

280 for high cancer exposures. Here, we investigated how these diverging patterns would evolve when

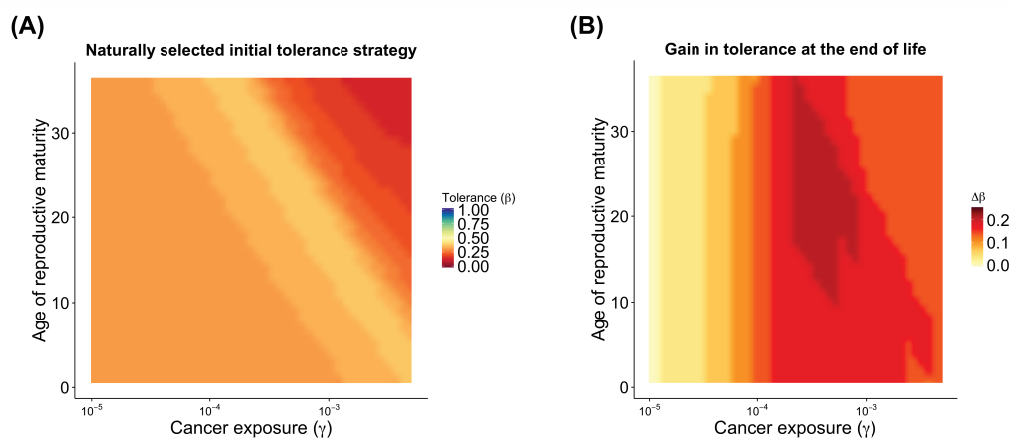
281 one is nested within the other, *i.e.*, how intrinsic (age of reproductive maturity) and extrinsic (cancer

282 exposure) factors may shape natural selection on resistance and tolerance to cancer, when both cells

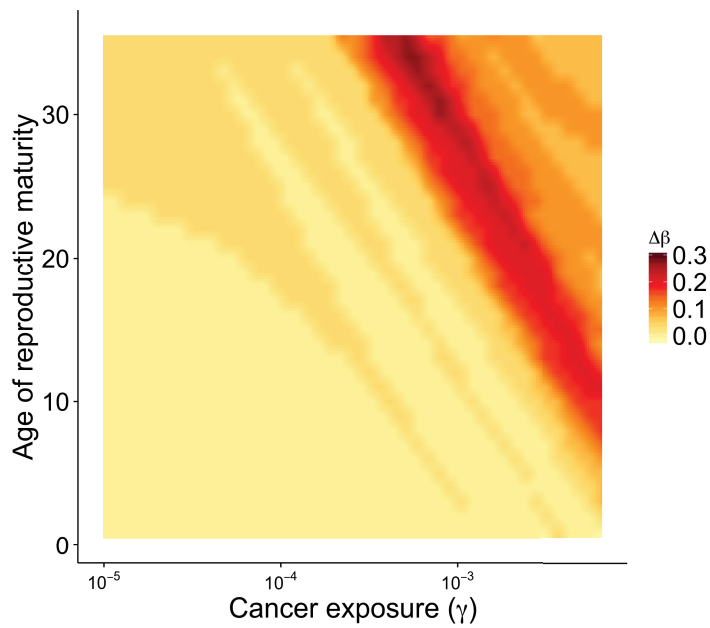
283 and organisms evolve.



284 Over the ranges of life histories and cancer exposures, the pattern of selection on resistance and  
 285 tolerance to cancer is actually similar whether healthy cells evolve during the organism's lifetime or  
 286 not (Fig. 3A when compared to Fig. 2A). However, compared with organisms in which they do not  
 287 evolve, healthy cells are initially more resistant in early life (Fig. 4), but select for more tolerance  
 288 during the organism's lifetime (Fig. 3B). Thus, organisms adapt to the evolution within them, since  
 289 they are selected for more resistance than they would need if healthy cells did not evolve. However,  
 290 the evolution of healthy cells is itself limited: the maximal tolerance that they can reach during an  
 291 organism's lifetime is lower than the strategy that they would adopt without inter-organism  
 292 evolution (cf. Fig. 1B).  
 293



294  
 295 **Figure 3: Influence of the age of reproductive maturity and cancer exposure on the nested evolution of**  
 296 **resistance and tolerance to cancer.** (A) Initial tolerance strategies of healthy cells at the organism's birth, after natural selection occurred.  
 297 The continuum of naturally selected strategies between full tolerance and full resistance is depicted in shades from red to violet: the reddest shades  
 298 account for resistant strategies, while the most violet shades represent tolerant strategies. (B) Gain in tolerance at the end of the life: the differential  
 299 between dominant strategies in the healthy cell pool at ages 0 and 70. Differences in tolerance are depicted in shades from yellow to red: the yellowest  
 300 shades account for low differences, and the reddest for high differences. Parameters used are reported in Tab. 1.  
 301

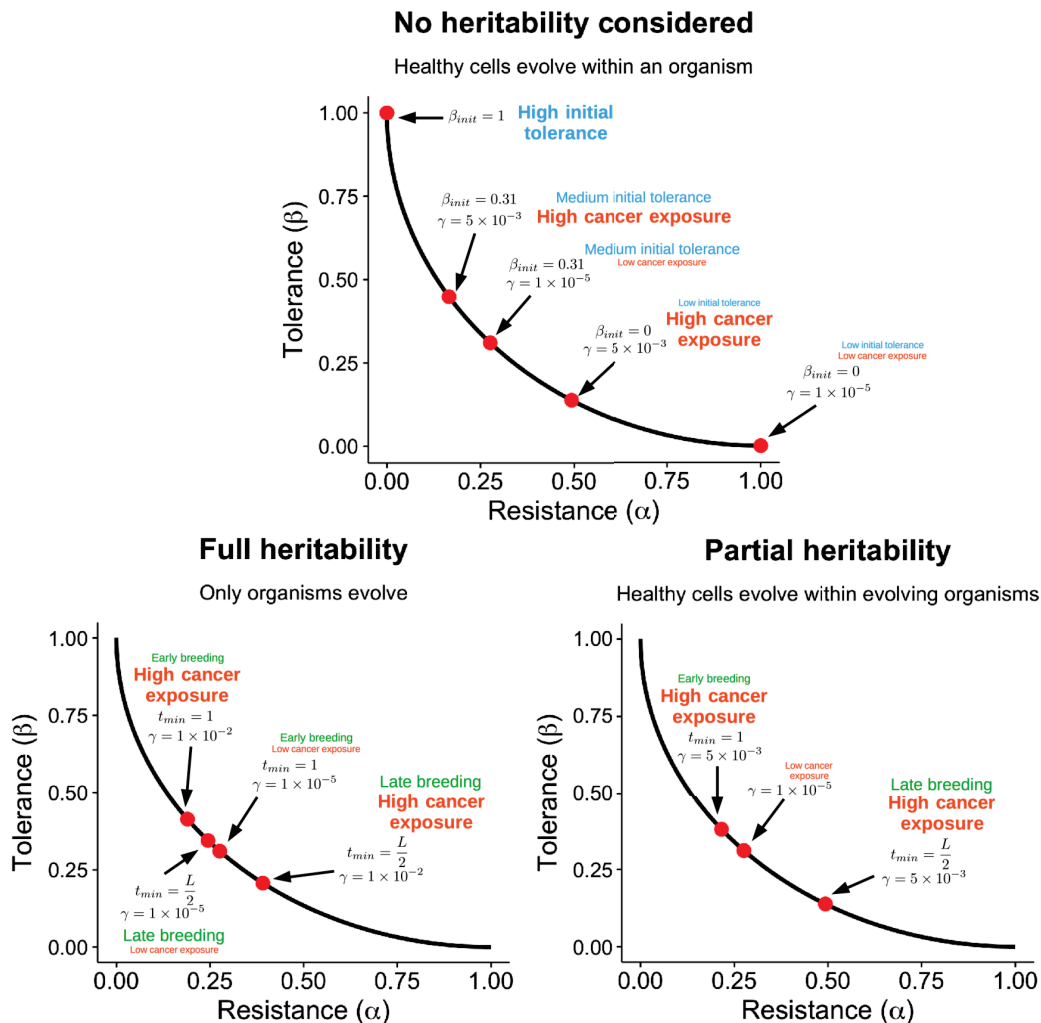


302

303 **Figure 4: Differences in the patterns of selection between the inter-organism model and the nested model**

304 **for the evolution of resistance and tolerance to cancer.** For same intrinsic and extrinsic conditions, we subtracted the initial  
 305 tolerance strategies selected in the nested model to the tolerance strategies selected in the simple inter-organism model. Differences in tolerance are  
 306 depicted in shades from yellow to red: the yellowest shades account for low differences, and the reddest for high differences. Parameters used are  
 307 reported in Tab. 1.

308



309

310 **Figure 5: Summary of the outcomes of natural selection on defenses against cancer, depending on the**

311 **heritability considered in each model.** When only the evolution of healthy cells is considered, no assumption is made on the heritability

312 of defense traits: in any case, cells evolve towards more tolerance. When organisms are the only one to evolve, defense traits are considered to be

313 fully heritable: resistance is only favored over tolerance for late-breeding organisms with high cancer exposure. When evolution is considered at both

314 scales, defense traits are thus only partially heritable: the pattern on selection is the same as when defense traits are fully heritable, but all strategies

315 are shifted towards resistance in early life.

316

#### 317 **4. Discussion**

318 In this study, we explored a gradient of defense strategies against cancer, which ranged from a full

319 investment in resistance to cancer to a full investment in tolerance to cancer. The evolution of these

320 strategies was followed in healthy cell populations and in pluricellular organism populations, either  
321 considered separately or simultaneously following a nested approach. Results are recapitulated in  
322 Figure 5.

323 At the intra-organism scale, we found that tolerance is favored over resistance (Fig. 1A). Whatever  
324 the initial phenotype, healthy cell populations are invaded by more tolerant strategies during an  
325 organism's lifetime. The higher cancer exposure is (*i.e.*, when more cancer cells emerge more  
326 quickly), the more tolerant strategies invade (Fig. 1A), and in a shorter lapse of time (Fig. 1B).  
327 Cancer therefore acts as a selective pressure on healthy cells, and favors tolerance as it allows  
328 higher persistence on the short term.

329 However, at the inter-organism scale, the relative investment between resistance and tolerance  
330 depends on the species' cancer exposure and life history (Fig. 2A). Indeed, resistance is favored  
331 over tolerance in late-reproducing species with the highest cancer risks, whereas tolerance is  
332 selected when cancer exposure is low or when organisms reproduce early. This can be explained by  
333 the influences of these strategies on survival. Tolerance supports the organism's survival on the  
334 short term, which explains why it is selected in early-breeding species. But on the long term, it also  
335 allows tumors to grow more (Fig. 2B). The efficiency of tolerance should not be affected when  
336 cancer is rare, but it would result in a quick increase of the organism's mortality when cancer is  
337 prevalent (Fig. 2C). Resistance, however, is only efficient because it reduces the load of sensitive  
338 cancer cells (Fig. 2B). Therefore, it is of little use when the cancer burden is low, *i.e.*, in early life or  
339 for low cancer exposures. Late-breeding organisms, when cancer risk is high, should benefit more  
340 from resistance than from tolerance (Fig. 2C).

341 By nesting these two scales within each other, we found that organisms win the conflict over their  
342 cells. When both organisms and their cells evolve, the resulting pattern of selection follows a  
343 pattern very similar to the one observed when healthy cells do not evolve (Fig. 3–4): resistance is  
344 favored over tolerance in late-breeding organisms highly exposed to cancer, while more tolerant  
345 strategies are selected in other cases. However, compared to when cells do not evolve, organisms

346 evolve to more extreme strategies: they are more resistant in early life (Fig. 3A and Fig. 4), and  
347 more tolerant in late life (Fig. 3B). The phenotypic plasticity of defense strategies shifts to more  
348 tolerance during the lifetime (Fig. 1). This phenomenon shifts natural selection to favor more  
349 resistance in early life.

350 Whereas healthy cells could evolve to maximal defense strategies (notably maximal tolerance), we  
351 found that organisms would not do so. The impossibility for organisms to evolve to maximal  
352 resistance/tolerance can be explained by the tradeoffs between resistance, tolerance and fertility,  
353 that we introduced in our model. This is opposite to host-parasite interactions: although organisms'  
354 defenses to parasites are also affected by similar tradeoffs as cancer, the hosts commonly evolve to  
355 the extrema of possible strategies (*i.e.*, either maximal or minimal resistance/tolerance, see van  
356 Baalen 1998; Gandon and Michalakis 2000; Donnelly et al. 2015; Kada and Lion 2015). Contrarily  
357 to horizontally transmitted parasites, cancer cells only interact with their host organism. Resistance  
358 and tolerance should not therefore influence their evolution over generations of organisms. Though,  
359 an organism's strategies may shape the evolution of its cancer cells during its lifetime. Cancer cells  
360 can actually evolve to escape resistance (Khong and Restifo 2002), but it is unsure whether  
361 immunoediting results in the selection of more aggressive variants or simply releases the immune  
362 pressure on cancer progression (Dunn et al. 2004). On the contrary, not only does tolerance allow  
363 cancer progression, but it might even promote it on the long term: (i) because the pathways  
364 involved in tissue repair are common to cancer progression (Beachy et al. 2004; Schäfer and Werner  
365 2008); (ii) because secretions which trigger healthy cell proliferation may do the same to  
366 malignancies (Harun et al. 2007; Sottnik et al. 2015). These intricate dynamics may together  
367 determine the efficiency of resistance and tolerance to mitigate the negative effects of cancer on  
368 fitness.

369 In this study, we considered cancer risk to be extrinsic and life history to be intrinsic to the  
370 organism. Though, depending on the species, several physiological and ecological processes may  
371 temper these assumptions. Despite extrinsic factors are accountable to up to 90% of cancer

372 development (Wu et al. 2016), intrinsic differences in the number of stem cell divisions (Tomasetti  
373 and Vogelstein 2015) and in cell division control (Abegglen et al. 2015) partly explain variations in  
374 cancer risk within and across organisms. Moreover, environment and cancer progression are  
375 involved in reciprocal interactions, that may influence both cancer risk and life history (Vittecoq et  
376 al. 2013). When exposed to cancer, organisms may adjust their behavior to impede cancer  
377 progression (Vittecoq et al. 2015) and their life history traits to palliate the cost of harboring a tumor  
378 (Ujvari et al. 2016a; Arnal et al. 2017). On the contrary, long-lived organisms are more exposed to  
379 cancer (Rozhok and DeGregori 2016), and interactions with other traits may allow genetic variants  
380 associated to higher cancer risk to persist in natural populations (Arnal et al. 2016). Further studies  
381 addressing the relative investment in resistance and tolerance to cancer should therefore pay  
382 attention to the evolutionary ecology of organs and species which they will focus on (see *e.g.*,  
383 (Thomas et al. 2016)).

384 Furthermore, intrinsic mechanisms being able to reduce the risk of developing a cancer, this raises  
385 the question of the diversity of defense strategies that organisms may evolve. Organisms have  
386 evolved many barriers to carcinogenesis (*e.g.*, apoptosis, contact inhibition, etc., see Gatenby and  
387 Gillies 2008), but whether these traits can be considered as resistance strategies should be  
388 discussed. Parasites are entities easy to distinguish from their hosts because of their antagonisms,  
389 consequently it is as well easy to define resistance as any trait of the host that will prevent parasitic  
390 survival/proliferation. Conversely, cancer cells are the result of a long, cumulative transformation,  
391 from healthy cells sharing common interests with the rest of the organism to malignant cells that  
392 thrive at the expense of their host. Thus, some traits, such as antitumor immunity, are easy to  
393 consider as resistance strategies, since they specifically target malignancies. But the barriers to  
394 carcinogenesis prevent the occurrence of malignancy: one should be tempted to define these  
395 mechanisms as avoidance, rather than resistance, strategies. We believe that further discussion  
396 should be granted on this topic for a better understanding of the evolution of defense strategies.

397 We employed a nested approach in order to take into account intricate eco-evolutionary dynamics of  
398 both organisms and (healthy and malignant) cells that they are made up of. So far, this approach has  
399 been used to address host-parasite coevolution (when the parasites evolve within their hosts, *e.g.*,  
400 Gilchrist and Coombs 2006), and transitions between levels of selection (*e.g.*, from unicellularity to  
401 pluricellularity, Michod 1996). The former use of this approach to study antagonistic interactions  
402 has already been discussed. Yet, it is to note that the impacts of cancer progression on organism  
403 fitness has been very poorly addressed (Vittecoq et al. 2013; Dillman and Schneider 2015), and that  
404 *in vivo* measures will be mandatory for further developments. Regarding the latter use of nested  
405 models in evolutionary biology, such an approach may highlight potential evolutionary conflicts at  
406 multiple scales. Indeed, we predicted tolerance to evolve to high levels in cell populations, but to  
407 much lower levels when selection occurs at an organism scale. This prediction can be explained by  
408 the fact that self-renewal is a selfish trait, whereas killing cancer cells benefits to the whole healthy  
409 cell population (Michod 1996; Michod and Roze 2001). In this context, the conflict between  
410 organisms and their cells for the investment on tolerance resembles to the conflict with cancer cells.  
411 Tolerance *in vivo* could be regulated by the same mechanisms that limit carcinogenesis (Vousden  
412 and Lane 2007), even though organism survival is likely to depend on healthy cell density.  
413 In this study, we addressed the evolution of natural defenses to cancer, using a nested approach to  
414 link the impacts of intra-organism evolution to inter-organism evolution. We notably found that the  
415 mechanisms evolved in organisms under cancer pressure do not necessarily favor the organism's  
416 survival (Kirkwood and Rose 1991). Novel therapeutic approaches could therefore consist in the  
417 stimulation of tolerance to cancer to prevent patient damage (Jansen et al. 2015).

418

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## 10 Une perspective multi-échelle sur les modifications phénotypiques associées au cancer

**Titre :** *Host manipulation by cancer cells: Expectations, facts, and therapeutic implications*

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# Host manipulation by cancer cells: Expectations, facts, and therapeutic implications

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Similar to parasites, cancer cells depend on their hosts for sustenance, proliferation and reproduction, exploiting the hosts for energy and resources, and thereby impairing their health and fitness. Because of this lifestyle similarity, it is predicted that cancer cells could, like numerous parasitic organisms, evolve the capacity to manipulate the phenotype of their hosts to increase their own fitness. We claim that the extent of this phenomenon and its therapeutic implications are, however, underappreciated. Here, we review and discuss what can be regarded as cases of host manipulation in the context of cancer development and progression. We elaborate on how acknowledging the applicability of these principles can offer novel therapeutic and preventive strategies. The manipulation of host phenotype by cancer cells is one more reason to adopt a Darwinian approach in cancer research.

## Keywords:

■ cancer cell; cancer progression; clinical oncology; host manipulation; parasitic ecology

## Introduction

It is now well established that cancer development and progression represent an evolutionary process as Darwinian selection drives cancer cells along evolutionary landscapes, culminating in resistance to immune attack, malignant progression, metastasis [1], and even sometimes contagion (Box 1). For this reason, insights into the evolutionary and adaptation dynamics of cancers can be gained by studying the evolutionary strategies of organisms, especially of those which follow a parasitic lifestyle [2–6]. In non-transmissible cancers, malignant cells are, at best, under selective pressures for this parasitic lifestyle for only a few decades, i.e. according to the somatic mutation theory each cancer must “reinvent the wheel” because their evolutionary products die with the host [7] (but see [8, 9]). Conversely, in the cases of contagious cancers, fitness is not restricted by host death, allowing for a longer evolutionary history involving coevolutionary processes with the host species [10]. Given this ecological and evolutionary context, theory postulates that lineages able, like classic parasitic organisms (see Box 2), to manipulate phenotypic traits in their host in ways that favor their

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## Abbreviations:

**CTVT**, canine transmissible venereal tumor; **DFTD**, Devil facial tumor disease.

**Box 1**

There are four examples of transmissible cancers: three mammalian (Devil facial tumor disease (DFTD), canine transmissible venereal tumor (CTVT), hamster-induced transmissible sarcoma) and one invertebrate (clam leukemia, CL) transmissible cancer cell lines have so far been identified. In these cases, cancer cells are

true infectious agents (i.e. they are contagious) and hence escape the demise of the host organism. Image of Syrian hamster taken by cdrussorusso (<https://www.flickr.com/photos/23516192@N08/>), and used under Creative Commons – Attribution 2.0 Generic License.

	Canine Venereal Tumour Disease (CTVT)	Devil Facial Tumour Disease (DFTD)	Contagious reticulum cell sarcoma (CRCS)	Clam leukaemia (CL)
<b>Species affected</b>	Dogs, wolves, coyotes and jackals	Tasmanian devil ( <i>Sarcophilus harrisi</i> )	Syrian hamster ( <i>Mesocricetus auratus</i> )	Soft-shell clams ( <i>Mya arenaria</i> )
<b>Appeared</b>	>10,000 years ago	>20 years ago	1960s	>40 years ago
<b>Distribution</b>	Worldwide	Tasmania	Laboratory colony	North Atlantic coast
<b>Cell of origin</b>	Myeloid cells	Schwann cells or precursors	Neoplastic histiocytes	Haemocytes
<b>Emerged due to</b>	Low genetic diversity of host species	Low genetic diversity of host species	Not known	Pollution, temperature, and overcrowding
<b>Spreads via</b>	Direct contact during sexual intercourse and licking of affected areas	Direct contact during social interaction (mating and fighting for food)	Subcutaneous implantation, feeding on the ulcerated tumours, cage contact, via mosquito bites	Filtration of seawater contaminated with neoplastic cells
<b>Primary tumours</b>	Genitalia	Face	Upper lip, subcutaneous	Haemolymph
<b>Metastasis</b>	Rare	70%	100%	100% (invade all tissues)
<b>Mortality</b>	Rare	Close to 100%	Animals were euthanized	Close to 100%
<b>Manipulation of the hosts' microenvironment</b>	Potential paracrine signalling and chemotaxis	Potential paracrine signalling and chemotaxis	Potential paracrine signalling and chemotaxis	Potential paracrine signalling and chemotaxis
<b>Manipulation for transmission</b>	Upregulates oestrogen receptors and increases the hosts' sexual receptiveness and attractiveness	Potentially influencing boldness/shyness	Not known	Not known

proliferation and/or transmission to novel hosts (for contagious cancers) should achieve higher fitness, and consequently be favored by selection. However, the existence of host manipulation by cancer cells has not been extensively studied until now, and/or has been envisaged in isolation from parasitological research.

### Host manipulation: What could we learn from classic parasites?

Not all phenotypic changes in parasitized hosts are parasitic manipulations: they may, variously, benefit the host (e.g. fever); benefit neither the host nor the parasite ("side-effects"); or benefit both the host and the parasite [11] (Box 3). As far as manipulation is concerned, parasitologists have identified three main evolutionary routes that can lead to this behavior: (i) manipulation *sensu stricto*; (ii) a mafia-like strategy; and (iii) exploitation of compensatory responses [12]. Route 1 is a decidedly manipulator-oriented view, while Routes 2 and 3 are scenarios in which the host genotype is also involved in the evolution of manipulation [13] (Box 3).

Manipulation *sensu stricto*, which is classically considered as the main manipulative process, proposes that host alterations that benefit the parasite are illustrations of the extended phenotype concept [14]: the altered host phenotype results from the expression of the parasite's genes. In this view, manipulator genes are selected for their effects on host phenotype. Parasites target at least four physiological systems that shape behavior in both invertebrates and vertebrates: neural, endocrine, neuromodulatory, and immunomodulatory [15–18].

Alternatively, "making the host do something" can sometimes be achieved when something is better than nothing for the host. In these situations, phenotypic changes in hosts can be the direct products of natural selection acting on the host genome, even when they result in significant fitness benefits for the parasite. In the context of mafia-like strategies (Route 2), parasites can select for collaborative behavior in their hosts by imposing extra fitness costs in the absence of compliance. By cooperating with manipulative parasites rather than resisting them, hosts might mitigate fitness costs associated with parasitism. The mafia-like strategy works from a theoretical point of view, but reports from natural settings are still scarce [19]: one such example is brood parasitism by cuckoos, in

## Box 2

## The outstanding diversity of host manipulation by parasites

Following the pioneer work of Bethel and Holmes [81], it is now well established that many parasitic organisms (e.g. virus, bacteria, fungi, protozoans, nematodes, nematormorphs, acanthocephalans, trematodes, cestodes, and insect parasitoids) have evolved the capacity to manipulate the phenotype of their hosts to increase their own probability of transmission and/or survival in a given host, or insure that their propagules will be released in an appropriate location or habitat (see reviews [13, 82–84]). Host manipulations are extremely diverse, ranging from small changes in the time allocated to some activities to the display of novel, sometimes multidimensional, phenotypic alterations that can impact behavior, physiology, and/or morphology [85].

**A:** A gypsy moth caterpillar (*Lymantria dispar*) killed by a baculovirus (left), along with a “not yet dead – zombie” caterpillar (right) (photo Forest Service of the United States Department of Agriculture). Infected caterpillars climb to treetops where they are liquefied shortly before they die and release a shower of infectious viral particles. This elevated mortuary position allows optimum dispersion for the parasite: infectious particles fall onto lower-level leaves and healthy caterpillars become infected when ingesting contaminated leaves. This is a striking example of manipulation *sensu stricto*: there is a single viral gene encoding a protein (EGT) which inhibits a hormone in the host inducing the tendency to climb up [86].

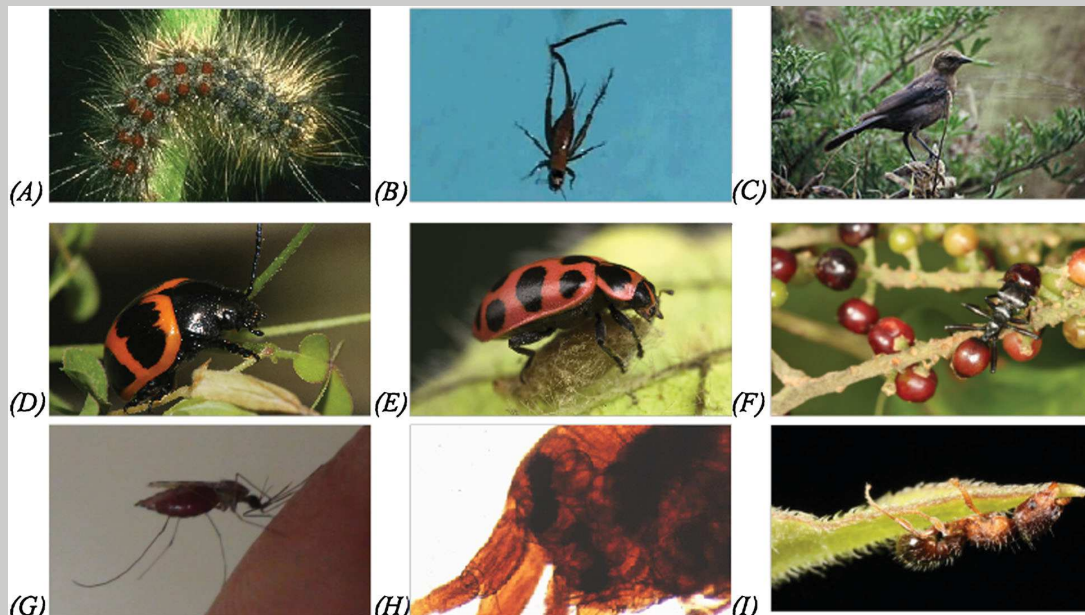
**B:** The Gordian worm (*Paragordius tricuspidatus*) exiting the body of a cricket (*Nemobius sylvestris*) (photo

F. Thomas). Infected crickets commit suicide by jumping into water, allowing the aquatic parasite to exit the host and find a mating partner [87]. This is another likely example of manipulation *sensu stricto*: proteomic analyses have revealed parasite production of molecules that may act directly on the cricket’s central nervous system [88].

**C:** The brown-headed cowbird (*Molothrus ater*, photo L. Karney, USFWS), a brood parasite, is a classic example of manipulation based on mafia-like strategies. By manipulating ejection of cowbird eggs and cowbird access to nests of their warbler host, Hoover and Robinson [89] showed that 56% of ejector-nests compared with only 6% of acceptor-nests were destroyed by cowbirds. In addition, the study found that warbler hosts produced significantly more offspring by accepting cowbird eggs. This mafia behavior therefore selects for collaborative hosts.

**D:** The leaf beetle host *Labidomera clivicollis* (photo Smidon33). In response to infection with the lifespan-reducing ectoparasite *Chrysomelobia labidomerae*, male beetles compensate for decreased longevity by engaging in more intense sexual behaviors which enhance both inter- and intra-sexual contacts (copulation and competition) [22]. This favors both the host, which maintains its fitness by increasing its mating rate, and the parasite, which achieves transmission to a greater number of hosts.

**E:** A manipulated beetle *Coleomegilla maculata* protecting the cocoon of the braconid wasp *Dinocampus*



*coccinellae* (photo with courtesy of P. Goetgheluck). Female wasps deposit a single egg in the hemocoel of the host, and during larval development the parasitoid feeds on host tissues. The larva keeps the host alive such that after emergence it becomes a bodyguard against natural enemies. Maure et al. [90] showed that protected parasitoid cocoons suffer less predation than unprotected cocoons. In addition, the length of the manipulation period is negatively correlated with parasitoid fecundity, providing evidence for a cost of manipulation.

**F:** The nematode parasite *Myrmeconema tropicum* turns the abdomen of its ant intermediate host *Cephalotes atratus* bright red, and drives the ant to go perch, with its abdomen raised, among patches of small red berries, to await the frugivorous birds that serve as definitive hosts for the nematode ([91], photo courtesy of S. Yanoviak). This is a typical example of simultaneous multidimensional manipulation: both the ant color and behaviors are manipulated.

**G:** The tsetse fly *Glossina morsitans morsitans*, a vector of several *Trypanosoma* species responsible for human sleeping sickness (photo T. Lefevre). Host manipulation by parasites may have profound significance for human health. Many manipulative parasites are responsible for devastating vector-borne diseases such as dengue fever, malaria, leishmaniasis, or sleeping sickness [92]. These parasites induce changes in the behaviors of their insect vectors that affect the frequency of interactions between hosts and vectors. The onset of behavioral changes are

synchronized with the parasite development. When the parasite is not fully mature, the contact rate with vertebrate hosts is reduced. Since biting is risky (e.g. host defensive behaviors can kill the vector and its parasite), reduced biting rate is beneficial to the parasite. In contrast, when the parasite is mature and ready to be transmitted, it modifies the behavior of its vector in a way that increases contact with the vertebrate host and hence transmission.

**H:** A cystacanth of the trophically transmitted acanthocephalan parasite *Polymorphus minutus* encysted in the body cavity of its intermediate crustacean host *Gammarus pulex* (photo F. Thomas). This parasite induces both simultaneous and sequential multidimensional manipulation. It modifies the crustacean geotactic and escape behaviors and thereby enhances the likelihood that the intermediate host is consumed by water bird definitive hosts. These changes do not occur before the parasite is mature and ready for transmission. Because premature predation would be fatal, parasites have evolved the ability to suppress predation on the intermediate host when uninfected to bird hosts.

**I:** An ant infected with the trematode *Dicrocoelium dendriticum* clamping down with its jaws on a grass tip (photo C. Eiseman). The parasite makes the ant leave its colony, cling to grass blades when dusk falls and wait for a herbivorous mammal (the definitive host). Photo D was taken by David Hill, and used under the Creative Commons – Attribution 2.0 Generic Licence. The photo was downloaded from <https://www.flickr.com/photos/dehill/9254286400/>.

which magpies that eject cuckoo eggs from the nest incur higher nest predation by cuckoos than those that accept parasite eggs [20].

Route 3 proposes that parasitic organisms affect fitness-related traits in the host to induce host compensatory

responses that, at least partially, match the parasite's needs [21]. Parasites can themselves be the causal agents of the compensatory responses displayed by the host, and/or directly exploit compensatory responses that have been selected in other contexts by mimicking the causes that

### Box 3

#### The three main types of manipulation among parasites (from [12])

##### 1. Manipulation sensu stricto

Host behavioral alteration may be regarded as a compelling illustration of the extended phenotype [14], that is, the expression of the parasite's genes in the host phenotype. The extended phenotype perspective thus postulates that in some host–parasite interactions, the parasite genes are responsible for the aberrant behavior. In this view, genes of the parasite are selected for altering host phenotype.

##### 2. Mafia-like manipulation

Host behavioral alteration may be regarded as a forced collaboration. Parasites may select for collaborative behavior in their hosts by imposing extra fitness costs in the absence of compliance. The parasite would be able to

adopt a plastic strategy (i.e. facultative virulence) depending on the level of collaboration displayed by the host. According to this theory, genes of the parasite are selected for their ability to detect non-collaborative behaviors and their ability to produce retaliatory behavior.

##### 3. Exploitation of host compensatory responses

Host behavioral alteration may be regarded as a host response to parasite-induced fitness costs. Parasites may affect fitness-related traits in their hosts such as fecundity and survival in order to stimulate host compensatory responses because these responses can increase parasitic transmission. Accordingly, genes of the parasite are selected for their pathological effects that induce a host compensatory response. Since behavioral changes both mitigate the costs of infection for the host and meet the objectives of the parasite in terms of transmission, natural selection is likely to favor all the genes involved in this interaction.



induce them. A potential example is the sexually transmitted ectoparasite *Chrysomelobia labidomerae* which parasitizes the beetle *Labidomera clivicollis*: infected males have lower survival than uninfected ones, but to compensate they exhibit increased sexual behaviors, which enhance opportunities for parasite transmission [22].

### Host manipulation by cancer cells: What are the facts and expectations?

In the case of transmissible cancers, it is theoretically expected that manipulative strategies similar to those of parasites could have evolved, provided that enough evolutionary time and variation in cancer cell lineages have been available for selection to favor such adaptations. In addition, manipulative strategies leading to fitness benefits inside the host will also be favored when they facilitate crucial steps in tumorigenesis (e.g. malignancies must establish, receive nutrients, evade destruction from the immune system, and disseminate to distant sites), especially because it would cost less to cancer cells to delegate these functions through manipulation. For non-transmissible cancers, only the latter situation is relevant. However, we expect some manipulative strategies to emerge during the course of cancer progression. Notably, prior to cancerous cells switching to carcinogenesis, they nurture mutualistic relationships with other healthy cells and ultimately with the host. These interactions involve coordination between cells and organs via signaling and communication pathways. Cancer cells could thus quickly reroute these pathways to respond to their own microenvironmental constraints [23]. These hijacked traits would therefore evolve as exaptations (sensu [24]) for cancer cells, i.e. they would serve functions for which they were not designed.

#### Cancer cells manipulate their microenvironment

Tumor development (carcinogenesis, progression, and metastasis) strongly depends on the microenvironmental conditions met by cancer cells [25]. When considering effects of microenvironmental changes on cell selection during oncogenesis, the extended phenotype provides a conceptual framework; alterations of the microenvironment are viewed as parts of the extended phenotype of cancer cells that influence the success of cancerous and precancerous cells during oncogenesis [26].

Interestingly, there is mounting evidence that many non-neoplastic host cells collaborate with the tumor, contributing to its development [27] by promoting and facilitating: (i) establishment and proliferation, (ii) immune response modulation, and (iii) metastases.

#### *Cancer cells manipulate their microenvironment to facilitate establishment and proliferation*

For instance, most enzymes involved in extra-cellular matrix breakdown are secreted by normal cells adjacent to the tumor site (i.e. cancer cells induce these changes and/or just

“free-ride” off normal cell physiology [28]). By producing growth factors and pro-inflammatory cytokines, normal cells are also involved in neoplastic transformation of cells and tumor clonal expansion [29]. Cancer cells send signals to induce epigenetic changes in surrounding stromal cells and recruit them to create a community of highly specialized cells able to sustain the needs of the tumor [2, 4, 30]. For example, the expression of the extracellular matrix metalloproteinase inducer (EMMPRIN) by cancer cells recruits fibroblast cells into the production of matrix metalloproteinases [31, 32]. In addition, stromal cells also release their own diffusible signals that themselves contribute to tumorigenic activities, participating in the recruitment of other stromal cells. For example, EMMPRIN promotes its own secretion in fibroblast cells [31]. Interestingly, growing evidence suggests that polyclonality in intestinal tumors may originate from the recruitment of normal cells into carcinogenesis by a single cell-of-origin [33, 34]. The benefits of polyclonality for cancer cells remain unclear, but could be associated with extensive cooperativity between cancer cells [35, 36].

#### *Cancer cells manipulate their microenvironment to evade immune recognition*

Tumor-infiltrating immune cells even reverse their normal function: instead of eliminating cancer cells, they protect them and have immunosuppressive effects in tumor environment [37, 38]. Indeed, cancer cells can actively manipulate immune cell function via secretion of tumor-specific miRNAs [39]. Additionally, innate immune cells promote angiogenesis by the production of growth factors and chemokines [38, 40], and in many cancers, the release of CXCL chemokines recruits endothelial cells into angiogenesis [41, 42].

#### *Cancer cells manipulate their microenvironment to facilitate metastasis*

During the metastatic process, paracrine signaling and chemotaxis between the soil (novel tissue) and the seed (malignant cell) lead to tissue tropism of metastatic cells and the invasion of specific organs [43]. Stromal environments accommodating novel tumors can arise by manipulation at each site of tumor metastasis [10, 44, 45]. However, an interesting question concerning both metastatic processes and transmissible cancers is whether the evolved (clonally selected) abnormal stromal cells (“fellow-travellers”), which provide an optimal niche for primary tumor cells, accompany the invasive malignant cells during invasion of new organs and/or other host organisms [10]. Further studies are needed to answer whether intra- and/or inter-individual metastatic cells have evolved to be self-sufficient (i.e. grow and spread without supporting stromal cells), or rather rely on manipulation to successfully establish in a novel habitat.

All these manipulations apparently rely on molecular cross-talk between cancerous and healthy cells to induce collaborative responses from healthy cells. Collaborative behavior may result because healthy cells are directly victim of manipulative molecules produced by cancer cells, or because they respond to fake signals produced by cancer cells in a way that favors tumor development. Thus, manipulation

sensu stricto and compensatory responses (Routes 1 and 3) seem to be the major ways by which cancer cells manipulate healthy cells in their microenvironment.

### Can cancer cells manipulate beyond the microenvironment?

Cancer cells could manipulate beyond their immediate environment, targeting other host traits to satisfy different needs, a phenomenon that could greatly favor malignant progression and metastasis. Such multidimensional manipulations, either sequential or simultaneous, could be achieved by different cells in the tumor because tumorigenesis typically leads to tumor compartments each having distinct functions that cooperate to establish tumors [46]. These multidimensional manipulations would not simply be a summation of multiple smaller effects, but instead a novel collective phenotype may arise. Below we discuss eating behaviors and sleep as possible research directions on this topic.

#### *Can cancer cells manipulate eating behaviors?*

Cancer progression is often influenced by diet parameters (e.g. calorie intake, energy balance, diet composition [47, 48]). For instance, high-fat and carbohydrate diets significantly exacerbate cancer proliferation [49, 50]. Reciprocally, calorie restriction is being heralded as the most potent broadly acting dietary regimen for suppressing carcinogenesis [50, 51]. Therefore, cancerous individuals potentially have (at certain periods during carcinogenesis) some control over tumor progression by adjusting their diet in ways that limit cell proliferation (i.e. self-medication). Alternatively, just as gut microbes have been hypothesized to manipulate host eating behavior to promote their fitness at the expense of host fitness (e.g. [52]), cancer cells could also potentially modify host appetite to benefit the tumor. Since the metabolism of cancer cells is very different from normal cells, different nutritional requirements could arise at different stages of cancer development and progression compared with healthy cells. To satisfy their needs, cancer cells could then induce cravings for foods that they specialize on or that give them fitness advantages in the competition with healthy cells; furthermore, cancer cells might be able to induce dysphoria until foods that enhance their fitness are consumed. As a possible research direction, related to the higher metabolic demand of cancer cells, tumor-bearing individuals might be motivated to consume high energy substances, e.g. sugar, as a compensatory response. Interestingly, alterations of eating behaviors (e.g. taste changes, increased satiety with delayed gastric emptying [53]) are frequently reported by cancer patients, but it is unknown whether they correspond to host adaptations aimed at limiting cancer progression, cancer cell manipulation, or pathological consequences without adaptive value. While an increasing number of studies suggest that our bodies are composed of diverse organisms (microbiota) competing for nutritional resources, we believe that cancer cells should be considered as full players in these interactions.

As with gut microbes (see [52]), eating manipulations by cancer cells could theoretically be achieved through various,

more or less direct, mechanisms. For instance, it could be done by influencing reward and satiety pathways, producing mood-altering toxins, modifying taste receptors, and hijacking the vagus nerve, i.e. the neural axis between the gut and the brain. From an evolutionary point of view, Routes 1 and 3 could be invoked for both gut microbes and cancer cells.

#### *Can cancer cells manipulate sleep?*

The biological functions of sleep are not fully understood, but several studies support the hypothesis that sleep duration is strongly associated with immune defense [54, 55]. For example, mammalian species that sleep longer also have lower levels of parasitic infections [56]. Given that one of the functions of the immune system is to recognize and eliminate altered cells including malignant ones [40], cancer resistance may have played a significant role in the evolution of sleep. Furthermore, variation in duration of the sleep/wakefulness cycle strongly influences the production of various hormones including melatonin, which are important anti-tumor agents [57]. Sleep disturbances are very common in people affected by cancer [58, 59]. Cancer patients (especially breast and ovarian cancer patients [60, 61]) show a reduced distinction between daytime and nighttime activities, suggesting circadian rhythm disruption. High rates of insomnia among patients with breast, gynecological and lung cancers are also frequently reported [62]. In parallel, it has been shown that fragmented sleep in mice speeds cancer growth, increases tumor aggressiveness, and reduces the immune system's ability to control cancer [63]. Similarly, severity of sleep apnea predicts aggressiveness of melanoma [64]. Although these sleep disorders may have a variety of causes, one possibility is a direct tumor effect on sleep cycles [62], mediated, for instance, via an influence of tumors on the secretion of the cytokines that modulate the sleep/wake cycle (i.e. Route 1). Because the symptoms are non-specific, it is unclear, at the moment, whether cancerous cells are more or less directly favored by selection through disrupting sleep, and/or if this is only a side-effect of being sick having coincidentally positive effects on carcinogenesis.

### Can contagious cancers manipulate for transmission?

Canine transmissible venereal tumor (CTVT) and Devil facial tumor disease (DFTD) are considered the two oldest naturally occurring cancer cell lines, having appeared approximately 11,000 and 20 years ago, respectively [65, 66]. Evidence suggests that the evolutionary history of these cancers has promoted the development and implementation of highly elaborate adaptive strategies that maintain reproductive potential in the hostile micro- (stroma) and macro- (host genotype) environment of their canine and Tasmanian devil hosts [67]. Interestingly, the coexistence of CTVT with its hosts for millennia also resulted in its apparent ability to manipulate host sexual receptiveness to enhance its chances of transmission. By increasing estrogen receptor expression, CTVT enhances neoplastic growth factor production in the progestational vagina, which maintains high vascularization

and nutrient flow, and facilitates neoplastic development [68]. Via modulating the local vaginal tissue environment and increasing estrogen receptor expression, CTVT may also manipulate the host's sexual attractiveness and receptiveness, by potentially regulating receptiveness signaling odors and altering estrus cycle timing. An interesting hypothesis to investigate is whether, by altering odor cues, CTVT actively encourages matings and hence transmission. Laboratory experiments have shown that upregulation of estrogen receptor activity in sexually receptive female mice mediates male risk-taking behavior, and reduces the males' aversive response to predators [69]. Additionally, estrogenic signaling is involved in social interactions and avoidance of conspecifics carrying pathogens or malignant cells [7, 70]. Therefore, activation of estrogen expression by CTVT may not only "create" bolder males ready to fight for mating success, but also to mate with cancer-carrying females. Interestingly, bite patterns and behavior of Tasmanian devils revealed that primary tumors occur predominantly inside the oral cavity, and submissive animals are less likely to develop DFTD. Transmission seems to occur via dominant individuals biting the tumors of other devils [71]. Whether DFTD manipulates devil behavior by altering the hormones responsible for boldness/shyness remains unknown.

### What are the therapeutic implications?

Knowing why, when, and how cancer cells manipulate their host could be very valuable in combating cancer. For infectious diseases, determining whether a manifestation benefits the host, the parasite, neither or both has important therapeutic implications [11]. The same logic applies to cancer. Clinicians and researchers have in fact for decades been implementing anti-manipulative strategies, e.g. in combating angiogenesis and immunosuppression, but more effort could be done in this direction. There is currently a pressing need to understand the selective pressures and proximate factors shaping the evolution of manipulative abilities in cancer cells, in order to successfully deal with their consequences. In addition to its direct impact on health, host manipulation by cancer cells can influence the rate of expansion of invasive cancers within and/or between hosts.

### Targeting and dismantling the cancer supportive microenvironment

By improving our knowledge of the proximate factors involved, certain therapies could target the effect of manipulative cancer cells on healthy cells. Dismantling the network of supportive-manipulated cells could also be achieved by directly or indirectly (via bacteria or viruses) eliminating the "traitor" normal cells. Thus, therapy could target the information flow between cancer and manipulated cells, to either disrupt communication or induce signals that switch these cells (e.g. immune cells) back to the war against cancer [72]. This would have the double desirable effect of impairing cancer progression and forcing cancer cells into developing costly adaptations [73]: either by increasing the

effort toward manipulation, or by selecting self-sufficient clones. If self-sufficiency could emerge for some functions, such as vasculogenic mimicry replacing or complementing angiogenesis [74, 75], for other (e.g. immune) functions cancer cells may be forced to manipulate host cells, and targeting these particular functions may serve to avoid recurrence. Further theoretical and experimental investigations are necessary to explore tumor responses, because we cannot presently reject the hypothesis that a given therapy could instead favor the selection of more aggressive clones and/or rapid metastasis (i.e. just as vaccination can select for virulence in pathogens [76]). Thus, identifying and targeting cancer cells primarily contributing to host manipulation, as well as non-neoplastic cells that are manipulated by, and collaborate with the tumor, could be crucial for treating malignant diseases.

### Targeting manipulative mechanisms

Another promising research direction is to explore the proximate mechanisms used by parasites that manipulate their hosts in a similar way to cancer cells. For instance, like developing tumors, the nematode *Trichinella spiralis* (an intra-multicellular parasite) needs to recruit new blood vessels toward the developing nurse cells to meet its ever-growing demand for nutrients. Phylogenetically unrelated parasites often increase the chances of their transmission by inducing similar phenotypic changes in their hosts (e.g. [77]). Because these convergent strategies rely more or less on the same biochemical precursors, it could be expected that such convergence also exists with cancer cells. Thus, therapies that target manipulative activities in parasites could be equally effective against manipulation by cancer cells (see [78]).

### Preventing invasive cancer initiation

Acknowledging that host manipulations by cancer cells exist is only the first step. The challenge will be to assess their influence on malignant progression, and to integrate them as a factor in the design of preventive strategies and/or cures. Developing tools for monitoring manipulative activities by cancer cells at all relevant scales should permit the identification of actual life periods when the risk of invasive cancer initiation is highest. We need to determine whether oncogenic progression, from precancerous lesions to metastasis, relies on a more or less constant/obligatory sequence of manipulative events, which could potentially be altered by adapted therapies.

### Conclusions and outlook

Is it possible to ignore host manipulation in cancer processes? The answer is clearly no: most, if not all cancers, strictly rely on host manipulation for their development. Because of this strong dependence on host manipulation, exploring the extent to which manipulation by cancer cells occurs during carcinogenesis is a legitimate question, and curative strategies could clearly be developed from this knowledge. As a scientific

field, host manipulation has, until recently, been addressed in relative isolation from other scientific disciplines. This probably explains why, despite the extensive efforts of parasitologists to study manipulative strategies, few studies have so far established parallels with cancer cell strategies. Another reason is that host manipulation by parasites has been usually considered in the context of transmission strategies, but transmissible cancers appear to be rare. As demonstrated above, cancerous cells should be further investigated from the viewpoint of how they manipulate their immediate microenvironment, and also how they influence host behavior. It also seems that the main modes used by parasites to achieve manipulation may all apply to cancer cells (except possibly mafia-like strategies, which are rare in true host-parasite systems). Manipulations by cancer cells rely on the exaptation of pre-existing signaling pathways. By this way, they recruit healthy cells, which then engage additional healthy cells to perform tasks requested by tumor cells [31, 38, 40]. Given that host manipulations by cancer cells are likely to be subtle, we strongly encourage researchers to systematically explore the myriad symptoms displayed by cancer patients in order to discover those that could be host manipulations versus those that are host defensive responses to the manipulation and/or non-adaptive pathological consequences (i.e. by-product of being unhealthy). Additionally, due to the huge number of non-genetic variables involved in tumorigenesis, the question arises as to whether evolution of host manipulation by cancer cells should be considered within the framework of phenotypic plasticity rather than in a purely genetic framework. Further studies would also be required to explore if different types of cancer have different manipulative abilities (e.g. if colon/gut cancer influences/manipulates host diet more than for instance lung cancer). Finally, to understand the evolution of host manipulation by cancer cells, one must consider the complete ecological context in which tumors evolve, notably the community of organisms that inhabit the host and that may have shared or conflicting interests regarding its exploitation [79]. Only such an approach will permit a true assessment of the selective pressures acting on cancerous cells to manipulate the host. For instance, cancer is fueled by deregulation of signaling pathways in control of cellular growth and proliferation, but these pathways are also targeted by infectious pathogens (e.g. [80]). Although throughout our paper, we made the assumption that oncogenic selection should be strong enough to result in convergent evolution in manipulative strategies, little or no evidence has been found to support our theory. Therefore, we must also question whether each and every cancer is able to re-invent this particular wheel (i.e. manipulation) in more or less the same way in every patient time after time, based on the Darwinian principle of random variation. Alternatively, we cannot exclude that there is an underlying program that cancer cells are able to access but which is normally repressed. Numerous authors have, for example, noted the similarities between placentation, wound-healing, and embryogenesis, on the one hand, and cancer on the other [8, 9], and conversely suggested that cancer is a tissue-based disease and proposed an alternative theory of carcinogenesis, i.e. the tissue organization field theory (TOFT [8]). Clearly under the TOFT theory,

cancer manipulative strategies would follow different evolutionary pathways. Because one single method or model cannot thoroughly describe host manipulation by cancer cells, researchers interested in these responses must engage in greater exchanges and collaborations with scientists from different disciplines.

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The hamster and clam images in Box 1, and panels A,B,D,G,H in Box 2 were updated on February 23, 2016. The respective image attributions in the text of Boxes 1 and 2 were also updated.

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## Partie V

# Discussion et perspectives

Les travaux exposés dans cette thèse se focalisent sur l'application de concepts issus des sciences de l'évolution à un objet biologique impliqué dans les sciences médicales. Travailler à l'interface de deux disciplines peut produire de nouvelles connaissances dans l'une comme dans l'autre. Ce chapitre sera donc consacré à : (i) une discussion des apports et des limites des travaux sus-cités dans le cadre de la médecine et des sciences de l'évolution ; (ii) des projets de recherche qui pourront être réalisés dans la continuité de cette thèse.

## 11 Discussion

Au cours de cette thèse, plusieurs échelles d'espace et de temps ont été abordées : des processus éco-évolutifs au sein des tumeurs, des processus éco-évolutifs au sein des populations, des impacts de la dynamique intra-individuelle sur l'évolution des populations, et des impacts de l'évolution des populations sur la dynamique intra-individuelle. Les thèmes abordés sont tout aussi divers : des impacts des interactions biologiques sur l'écologie et l'évolution des cellules cancéreuses, de l'évolution neutre d'allèles de susceptibilité au cancer, et de la sélection à plusieurs échelles de la résistance et de la tolérance au cancer. Chacun de ces travaux a déjà été discuté dans son chapitre respectif. Du fait d'un objet d'étude commun (le cancer) et de l'utilisation de concepts communs pour décrire des dynamiques différentes, cette section abordera néanmoins les apports et les limites de cette thèse, dans le cadre de la biologie du cancer et des sciences de l'évolution.

### 11.1 Le cancer au cœur des dynamiques éco-évolutives

Le caractère progressif et multi-étapes de l'évolution du cancer rend particulièrement pertinente l'étude de sa dynamique éco-évolutive. La dynamique de progression du cancer est, à son tour, susceptible d'influencer la dynamique éco-évolutive de nombreux caractères portés par les organismes. Parmi ces caractères, ceux qui modulent la résistance ou la susceptibilité au cancer peuvent eux-mêmes influencer la dynamique de progression du cancer.

**Le rôle structurant des interactions** Le rôle des interactions biologiques a été de nombreuses fois abordé au cours de cette thèse : au sein des tumeurs dans les sections 5, 6, 9 et 10 ; entre le cancer et l'organisme dans les sections 7, 8, 9 et 10 ; au sein des populations d'organismes dans les sections 7 et 9. Dans les sciences de l'écologie et de l'évolution, les interactions biologiques sont largement connues comme participant à structurer les écosystèmes et les communautés d'une part, et les caractères phénotypiques des individus d'autre part. Les processus écologiques et évolutifs impliquant le cancer tendent à confirmer ce rôle.

Les sections 5 et 6 ont particulièrement discuté l'importance des interactions biologiques dans l'émergence et le maintien de la diversité génétique et phénotypique au sein des écosystèmes tumoraux. La section 5 a listé plusieurs exemples concrets et cas théoriques où les effets non-cellule-autonomes pourraient favoriser la diversité. Cette tendance se retrouve généralement dans les écosystèmes macroscopiques, où les interactions biologiques favorisent l'émergence de la diversité spatiale, génétique et phénotypique. Les interactions mutuellement avantageuses (mutualisme) ou néfastes (compétition) tendent ainsi à favoriser l'émergence et le maintien de phénotypes exploitant des niches spécialisées : les

partenaires mutualistes maximisent ainsi les échanges de sous-produits (Nico Blüthgen, Menzel, and Nils Blüthgen 2006; Guimarães Jr. et al. 2006), et les compétiteurs minimisent la concurrence dans l'exploitation des ressources (principe d'exclusion compétitive, Gause, Nastukova, and Alpatov 1934 et déplacement de caractère, Schluter, T. D. Price, and Grant 1984). De même, au sein des interactions antagonistes, l'adaptation réciproque des proies (hôtes) et prédateurs (parasites) (J Maynard Smith 1976) favorise l'émergence de nouveaux phénotypes d'une part ; l'effet *top-down* des parasites et prédateurs sur le réseau trophique stabilise les interactions et favorise la coexistence (Paine 1966).

Au contraire de toutes ces observations, les travaux de la section 6 démontrent une association inversée : dans les populations clonales en expansion, les interactions biologiques, lorsque fréquence- et densité-indépendantes, sont associées à une plus faible diversité génétique. Cette tendance ne se retrouve pas pour d'autres processus densité-indépendants (Abrams 2001). En revanche, il est possible que cette réduction de la diversité soit due à la dynamique d'expansion de la population (Waters, Fraser, and Hewitt 2013) : si les premiers clones à émerger ont une interférence négative sur la croissance des autres clones, alors la diversité devrait émerger plus lentement qu'en l'absence d'interactions. En outre, la connectance des réseaux d'interactions semble être un facteur déterminant dans le maintien de la diversité (Dunne, R. J. Williams, and Martinez 2002). La plupart des études ayant démontré un impact positif des interactions sur la diversité se sont focalisées sur un petit nombre de clones, impliquant nécessairement une forte connectance. Les simulations de la section 6 ont parfois impliqué plusieurs centaines de clones, pour lesquels de plus fortes variations dans la connectance peuvent avoir lieu.

Les sections 7, 8, 9 et 10 ont particulièrement discuté le rôle des interactions biologiques dans l'évolution de différents caractères génétiques et phénotypiques chez les organismes. Comme exposé ci-avant, les interactions biologiques contraignent la dynamique écologique des espèces, qu'elles favorisent ou non la croissance des populations. Dans de nombreux cas, l'apparition de nouveaux caractères au cours de l'évolution d'une espèce est une réponse adaptative à l'une de ces contraintes. Dans le cadre de l'interaction antagoniste entre les cellules cancéreuses et l'organisme, j'ai ainsi pu démontrer la possibilité d'équilibres éco-évolutifs stables pour des stratégies de défense de l'organisme (section 9), et de zones d'équilibre neutre pour des allèles pro-oncogéniques (section 8). Néanmoins, plusieurs zones d'ombre pèsent encore sur la contrainte réellement exercée par le cancer sur les organismes. En particulier, la dynamique de la perte de valeur sélective individuelle causée par le cancer est particulièrement difficile à déterminer (Marion Vittecoq et al. 2013). Faute de consensus clair sur la question, les sections 8 et 9 ont utilisé des mesures *ad hoc*, inspirées de modèles de coévolution hôte-parasite (p. ex. André and Gandon 2006; Antia, B. R. Levin, and May 1994) : le cancer a pu être considéré comme diminuant la fécondité (section 8) ou la survie (section 9), et de manière liminale (section 8) ou continue (section 9). Bien que nécessaire pour la poursuite des recherches sur l'évolution des organismes face au cancer, la quantification des impacts du cancer sur la valeur sélective devrait être particulièrement difficile : (i) parce que ces impacts pourraient avoir lieu pour un nombre de lésions cancéreuses difficile à détecter ; (ii) parce que cet impact est déjà tempéré par les mécanismes de défense qui ont été sélectionnés au cours de l'évolution (p. ex. Dillman and Schneider 2015).

**Neutralisme et mutations délétères** La place des mutations délétères dans les processus évolutifs a été le cœur de nombreux débats dans les sciences de l'évolution, notamment entre neutralistes et adaptationnistes. Le développement de l'évolution moléculaire et de la biologie évolutive du développement ont participé à démontrer l'importance des allèles neutres et faiblement délétères au cours de l'évolution. Les travaux exposés dans cette thèse (les sections 6, 7 et 8 notamment) proposent de nouvelles perspectives sur l'importance de l'évolution neutre dans le cancer.

La plupart des allèles délétères se maintiennent généralement à de faibles fréquences dans les populations : ces allèles s'accumulent au gré des mutations, et disparaissent au gré de la sélection et de la dérive.



Certains allèles peuvent se maintenir à des fréquences plus élevées que l'équilibre mutation-sélection, s'ils n'expriment leurs effets délétères que tard dans la vie (Medawar 1952) et/ou si leur pléiotropie leur confère des effets bénéfiques susceptibles de compenser leurs effets délétères (G. C. Williams 1957) : ces effets peuvent se retrouver dans le cas de plusieurs allèles pro-oncogéniques (Fernandez and Bowser 2010; K. R. Smith et al. 2012). Les travaux exposés dans les sections 7 et 8 suggèrent qu'un autre mécanisme évolutif pourrait favoriser l'accumulation de ces allèles dans les populations. En effet, lorsqu'un allèle est faiblement délétère, alors il est expurgé de la population moins vite qu'il n'apparaît, et peut donc se maintenir dans la population au gré de la dérive (équilibre mutation-dérive, Kimura 1968). Ainsi, dans les environnements fortement cancérigènes, la sélection de mécanismes de suppression du cancer peut neutraliser les effets délétères d'allèles pro-oncogéniques, et les autoriser à persister dans les populations. Si des allèles fortement délétères peuvent se maintenir par évolution neutre, alors il est possible que les allèles fortement délétères soient plus nombreux dans le génome des organismes. Selon cette hypothèse, il serait même possible que se produise une assimilation génétique d'allèles délétères (Waddington 1953) : dans des environnements cancérigènes, certaines populations pourraient accumuler des allèles pro-oncogéniques. Néanmoins, cette hypothèse reste difficile à démontrer empiriquement, car il faut démontrer que de tels allèles : (i) sont effectivement à l'équilibre mutation-dérive de manière stable ; (ii) retourneraient à l'équilibre mutation-sélection en l'absence de mécanismes de compensation intrinsèque.

Les travaux présentés dans la section 6 semblent indiquer que le maintien d'allèles délétères dans les populations pourrait également être autorisé par une compensation extrinsèque. En effet, au sein des tumeurs, la grande majorité des mutations sont neutres ou faiblement délétères (mutations *passengers*, Vogelstein, Papadopoulos, et al. 2013), et persistent au gré de la dérive (M. J. Williams et al. 2016; C.-I. Wu et al. 2016). Néanmoins, les interactions biologiques entre variants génétiques (notamment les interactions coopératives, Marco Archetti, Ferraro, and Gerhard Christofori 2015) semblent favoriser le maintien d'allèles fortement délétères, dont la persistance dans les tumeurs n'est autorisée que par leur compensation par des processus non-cellule-autonomes. Ces allèles fortement délétères pourraient participer de manière significative au potentiel d'adaptation de la tumeur aux changements de conditions micro-environnementales (notamment en cas de traitement, Gatenby, Silva, et al. 2009). Toutefois, au contraire des mécanismes de compensation intrinsèque exposés plus haut, la compensation extrinsèque dépend d'un réseau d'interactions, et donc de l'intérêt d'autres cellules ou individus. Il serait donc intéressant d'identifier si le maintien d'une diversité neutre au sein des tumeurs relève effectivement de la simple dérive, ou s'il s'agit d'une stratégie adaptative de *bet-hedging* (Frédéric Thomas, Ujvari, Gidoin, et al. 2017).

**Phénotype et évolution intra-organisme** Les sections 9 et 10 ont abordé les effets de l'évolution intra-organisme – des cellules cancéreuses et des cellules saines – sur le phénotype des organismes. Il est essentiel d'identifier les causes de cette plasticité du phénotype, c'est à dire quel(s) processus évolutifs en sont à l'origine, et ainsi d'identifier ses impacts sur l'évolution des organismes.

Jusqu'à présent, de nombreux caractères et/ou comportements ont été associés au cancer. Les travaux présentés dans la section 10 suggèrent que les cellules cancéreuses sont capables de modifier de nombreux caractères phénotypiques à leur avantage. Si la plupart de ces caractères sont micro-environnementaux, le cancer semble tout de même capable de manipuler la physiologie de l'organisme dans certains cas (p. ex. la lipidémie, J. Huang et al. 2016). Si le cancer est capable de manipuler certains caractères à son avantage, alors il est possible que certains de ces changements s'expriment dès les stades subcliniques. Il serait donc envisageable de considérer une inversion de la causalité pour certains caractères généralement considérés comme augmentant le risque de cancer (p. ex. Césarini 2007; Vucenik and Stains 2012) : par exemple, le cancer pourrait être la cause d'une alimentation riche en

glucides, et non pas la conséquence de ce comportement. Néanmoins, de manière générale, il n'est pas possible d'affirmer que les caractères associés au cancer sont toujours le résultat d'une manipulation de l'organisme. D'une part, au delà du micro-environnement, la plupart des mécanismes potentiels de manipulation de l'organisme par les cellules cancéreuses sont inconnus : il est donc plus probable qu'une modification complexe du phénotype soit le fait de l'organisme lui-même (Ujvari, Beckmann, et al. 2016), plutôt que des cellules cancéreuses. D'autre part, pour une modification phénotypique qui serait effectivement causée par les cellules cancéreuses, il n'est pas certain qu'elle leur soit adaptative (condition nécessaire pour qualifier le phénomène de manipulation, Hughes, Brodeur, and Frédéric Thomas 2012). Cette modification phénotypique pourrait être non adaptative (p. ex. la cachexie de l'organisme, Tisdale 2002), voire maladaptative (p. ex. l'activation du système immunitaire adaptatif par les cellules cancéreuses, Visser, Eichten, and Coussens 2006). En outre, sans manipuler son hôte, une cellule cancéreuse peut exploiter les sous-produits des modifications phénotypiques de l'organisme : toute modification phénotypique avantageuse pour la cellule cancéreuse n'est donc pas nécessairement de la manipulation. L'identification des causes et des conséquences des changements phénotypiques associés au cancer devrait permettre d'identifier comment le cancer contraint l'évolution des organismes multicellulaires.

L'évolution intra-organisme ne se limite pas aux cellules cancéreuses, mais peut également concerner les cellules saines de l'organisme. Les travaux présentés dans la section 9 incluent ce phénomène dans le but d'identifier les potentielles différences entre les stratégies de l'organisme et celles des cellules saines par rapport à la même contrainte du cancer. Ce modèle prédit que les cellules saines devraient être sélectionnées pour davantage de tolérance (c'est à dire de réplication cellulaire) que l'organisme tout entier. L'évolution intra-organisme devrait donc contraindre l'évolution des organismes vers moins de tolérance, afin de compenser le gain de tolérance durant la vie de l'organisme. De manière générale, on peut en déduire que les organismes devraient s'adapter à leur propre plasticité phénotypique. Néanmoins, en réalité, la sélection naturelle ne devrait que rarement favoriser la solution proposée dans la section 9, c'est à dire la sélection de phénotypes initiaux sub-optimaux. En effet, il peut exister de fortes variations temporelles dans l'exposition à des contraintes telles que le cancer, et il n'est donc pas assuré que la stratégie exprimée par l'organisme soit optimale au moment où il est exposé au cancer. Il est bien plus probable que les organismes évoluent vers une régulation de la plasticité phénotypique, comme dans le cas des mécanismes de suppression du cancer (DeGregori 2011; Nunney 2013). L'évolution intra-organisme des cellules saines devrait donc être orientée par un programme génétique hérité, davantage que par la sélection naturelle.

## 11.2 Sciences de l'évolution et oncologie

Les sciences de l'évolution peuvent participer à comprendre les origines du cancer en tant que pathologie. En effet, il est, d'une part, possible de prédire les conditions d'émergence de cette pathologie en recherchant les facteurs qui peuvent favoriser l'évolution de la prolifération cellulaire incontrôlée (Marusyk and DeGregori 2008). D'autre part, il existe des variations, plus ou moins importantes, dans la susceptibilité au cancer de certaines lignées et populations : celles-ci dépendent avant tout de l'histoire évolutive de ces lignées (Aktipis, Boddy, Jansen, et al. 2015), et des conditions écologiques dans lesquelles ces populations vivent (Hochberg and Noble 2017; Madsen et al. 2017). Ces connaissances peuvent contribuer à façonner des mesures prophylactiques et pronostiques. En outre, l'initiation et la progression du cancer suivent une dynamique qui peut être décrite selon des processus écologiques et évolutifs. Connaître et comprendre comment perturber ces processus devraient permettre d'identifier des stratégies pour endiguer, voire éliminer le processus cancéreux (Korolev, Joao B Xavier, and Gore 2014).

**Sciences de l'évolution, prophylaxie et pronostic** Des facteurs intrinsèques ou extrinsèques à l'organisme peuvent favoriser la transformation de cellules saines en cellules cancéreuses, lesquelles ensuite vivent et évoluent dans un environnement qu'elles façonnent (section 5). Connaître et comprendre lesquels de ces facteurs participent significativement à l'émergence de ces phénotypes peut donc offrir des mesures de prophylaxie et de pronostic, et ainsi orienter les pratiques médicales.

Les susceptibilités génétiques peuvent faire partie des facteurs qui favorisent l'émergence de cancer. Ainsi, jusqu'à 70% des femmes porteuses du variant oncogénique du gène *brca1* développent un cancer du sein avant leurs 70 ans (Brose et al. 2002). La principale mesure prophylactique contre ce risque de cancer est le dépistage génétique, suivi d'une potentielle ablation préventive des organes concernés (Eisen et al. 2005). L'identification de contextes à risque permettrait d'étendre ce dépistage à des populations encore non identifiées. Les travaux exposés dans les sections 7 et 8 suggèrent des contextes écologiques qui pourraient favoriser la présence de telles susceptibilités génétiques dans certaines populations. Notamment, une exposition soutenue à des causes de mortalité extrinsèque (maladies infectieuses, famines, violence) et à des facteurs cancérigènes (pollution, infections virales) devraient sélectionner des mécanismes de suppression du cancer, susceptibles ensuite de favoriser la transmission héréditaire d'allèles pro-oncogéniques. Les populations concernées dans leur passé plus ou moins lointain devraient porter ces allèles à plus haute fréquence que le reste de la population.

Toutefois, la vérification empirique de cette hypothèse doit remplir plusieurs conditions. D'une part, les mécanismes de suppression du cancer devraient être suffisamment puissants pour neutraliser l'effet des allèles pro-oncogéniques. Une étude historique serait donc nécessaire pour déterminer que l'espérance de vie moyenne passée a pu être inférieure ou égale à l'âge moyen auquel les cancers héréditaires se déclarent (ce qui semble être le cas, Galor and Moav 2007). D'autre part, cette hypothèse suppose une compensation intrinsèque des allèles pro-oncogéniques. Une étude de génétique des populations et de coalescence serait donc également nécessaire pour déterminer que les contextes écologiques identifiés ne créent pas de goulets d'étranglement, qui seraient susceptibles de favoriser la transmission par auto-stop de ces allèles (Ferla et al. 2007).

Les travaux présentés dans cette thèse suggèrent également des mesures de pronostic une fois que le cancer s'est établi (sections 5, 6 et 9). En effet, les interactions entre cellules cancéreuses (section 5 et 6) et avec l'organisme (section 9) participent à déterminer l'évolution de la tumeur. Au cours de cette thèse, j'ai notamment démontré une corrélation négative entre la fréquence des interactions entre cellules cancéreuses et l'hétérogénéité génétique des tumeurs (section 6). Connaître la fréquence des interactions dans une tumeur pourrait donc permettre de prédire son hétérogénéité, et *in extenso* son risque d'agressivité, de métastase et de récurrence post-thérapeutique (Maley, Galipeau, Finley, et al. 2006; Marusyk and Polyak 2010; Pribluda, Cruz, and Jackson 2015). Cependant, comme cité plus haut (section 11.1), cette corrélation reste à confirmer par d'autres mesures, notamment de connectance. De plus, l'identification des interactions entre cellules demanderait la réalisation systématique de biopsies et d'études cytologiques, à moins de pouvoir relier chaque interaction à une mutation spécifique, ce qui autoriserait le dépistage génomique.

Par ailleurs, la réaction physiologique de l'organisme face à la tumeur (résistance et tolérance, section 9) module la composition de la tumeur, et l'espérance de vie de l'organisme. Cette réaction pourrait également être utilisée comme facteur pronostic. Néanmoins, dans les travaux présentés, ces effets dépendent du taux d'apparition des cellules cancéreuses. Il est donc possible qu'une même mesure soit à l'origine de pronostics complètement différents selon l'âge du patient.

**Sciences de l'évolution et thérapeutique** Les sections 5, 9 et 10 suggèrent plusieurs pistes thérapeutiques dont le principe repose sur la connaissance de l'écologie évolutive des tumeurs et/ou sur l'écologie évolutive des organismes. Notamment, il serait possible de perturber les conditions biotiques et abio-

tiques des tumeurs pour provoquer l'effondrement de l'écosystème ou en modifier la composition génétique et phénotypique. De plus, il devrait être possible d'établir les conditions favorisant la survie du patient.

Ainsi, comme suggéré dans les sections 5 et 10, il devrait être possible de développer des thérapies visant à détourner la niche générée par les cellules cancéreuses : soit en régulant la disponibilité des biens publics (p. ex. les facteurs de croissance, S. A. Levin 2014), soit en éliminant préférentiellement les cellules productrices (Hanahan and Coussens 2012). Quelle que soit la solution envisagée, toute modification du réseau d'interactions au sein de l'écosystème tumoral est susceptible de modifier le régime de sélection sur les cellules cancéreuses. Restreindre les interactions pourrait, par exemple, favoriser une augmentation de l'hétérogénéité intratumorale (section 6). Aussi, plusieurs auteurs ont suggéré de manipuler le micro-environnement pour sélectionner les cellules cancéreuses les plus vulnérables possibles (Enriquez-Navas, Kam, et al. 2016; Lineweaver, Davies, and M. D. Vincent 2014; McFarland, Mirny, and Korolev 2014). Dans tous les cas, une connaissance approfondie de l'écosystème tumoral est essentielle avant que soit mise en place la moindre perturbation. En effet, la perturbation des écosystèmes favorise généralement la re-colonisation par les espèces envahissantes (Buckley, Bolker, and Rees 2007; Hobbs and Huenneke 1992) : la perturbation des réseaux d'interactions au sein de la tumeur est donc susceptible de favoriser les cellules cancéreuses les plus agressives (Gatenby 2009).

De manière générale doivent être favorisées les stratégies thérapeutiques qui visent à améliorer la condition du patient. Par exemple, la section 10 suggère une élimination thérapeutique des cellules saines manipulées par les cellules cancéreuses. Mais cette stratégie a peu de chances d'être applicable, car une élimination non ciblée de toutes les cellules d'un même type (p. ex. les fibroblastes) pourrait considérablement détériorer la santé du patient. Au contraire, la section 9 suggère d'envisager des stratégies thérapeutiques qui ne soient pas nécessairement curatives, mais qui viseraient avant tout à augmenter la tolérance du patient à sa pathologie. De manière générale, une augmentation artificielle de la tolérance à une pathologie pourrait permettre d'allonger la durée de vie des patients : ainsi, cette stratégie est de plus en plus envisagée pour les maladies infectieuses (Vale, Fenton, and S. P. Brown 2014), et pourrait être appliquée au cas du cancer (Jansen, Gatenby, and Aktipis 2015). Il est à noter que favoriser la tolérance du patient n'est pas incompatible avec des stratégies thérapeutiques visant à supprimer la tumeur : ainsi, il serait possible de réduire la taille de la tumeur, tout en compensant ses dégâts sur l'organisme. Cette stratégie est prometteuse, mais pourrait être limitée par plusieurs facteurs. Bien que l'on sache que des mécanismes de tolérance au cancer existent (Dillman and Schneider 2015), l'ensemble des mécanismes responsables et leur part relative n'ont pas encore été identifiés jusqu'ici. De plus, plusieurs indices semblent montrer que les cellules cancéreuses pourraient être favorisées par certains mécanismes de tolérance (Harun et al. 2007; Sottnik et al. 2015) : la stimulation artificielle de la tolérance pourrait donc par là-même réduire la survie du patient. Ce sont autant de facteurs qui appellent à identifier clairement les relations fonctionnelles et évolutives entre la tumeur et l'organisme.

## 12 Perspectives

Les travaux présentés dans cette thèse brassent de nombreuses thématiques, de nombreuses approches, et de nombreuses échelles. Dans cette section, je propose plusieurs perspectives de recherche que je souhaiterais développer dans la continuité de cette thèse. De même que dans cette thèse, les thèmes de recherche que je propose d'aborder à l'avenir concernent l'application de concepts d'écologie évolutive à la biologie du cancer, les interactions entre organismes et cancer dans une perspective évolutionniste, et l'approche multi-échelle des processus écologiques et évolutifs.

## 12.1 La métastase ou l'évolution de la dispersion

Au fur et à mesure que la tumeur croît et envahit les tissus avoisinants, les cellules au contact de vaisseaux s'y déversent et rejoignent les circulations sanguines et lymphatiques. Ces cellules tumorales circulantes sont susceptibles de se fixer dans de nouveaux tissus, à distance de la tumeur primaire, et de générer de nouvelles tumeurs : des métastases. Ce processus peut s'expliquer simplement d'un point de vue physiologique : (i) sous la pression exercée par la croissance tumorale, des cellules sont évacuées dans la circulation avoisinante ; (ii) celles-ci se fixent éventuellement aux tissus pour lesquels la capacité d'adhésion est la plus grande ; (iii) leur capacité proliférative se poursuit dans ce nouveau substrat. Néanmoins, les cellules cancéreuses sont des unités de sélection, et la tumeur un écosystème : la dynamique de la métastase pourrait donc être expliquée comme un caractère adaptatif pour la tumeur.

Les cellules cancéreuses prolifèrent initialement dans un micro-environnement qui ne leur est pas favorable. La progression cancéreuse est justement basée sur la permissivisation du micro-environnement, donc sur la modification de l'écosystème vers une forme qui sera de plus en plus favorable aux cellules cancéreuses. En ce sens, la tumorigenèse est un phénomène comparable à une *succession écologique* (Kareva 2015). L'invasion des tissus avoisinants correspondrait dans ce cas au stade climacique de l'écosystème tumoral. Si le processus métastatique commence bien avant ce stade, il semble donc prendre de l'ampleur lorsque la tumeur primaire termine sa succession. Ceci peut être compris comme une stratégie de dispersion de la part de la tumeur : les individus sont sélectionnés pour augmenter le taux de dispersion de leurs descendants au fur et à mesure que l'écosystème vieillit (Ronce et al. 2005). Cette stratégie de dispersion est d'autant plus importante que l'apparement est fort entre les individus (Bittume et al. 2013).

Une perspective de cette thèse est donc de déterminer (i) si la métastase peut s'expliquer comme un processus adaptatif pour les cellules cancéreuses, et (ii) si cette adaptation peut être expliquée par les mêmes causes que celles qui déterminent l'évolution de la dispersion dans les écosystèmes macroscopiques. Pour ce faire, il sera nécessaire de modéliser le coût de la compétition entre cellules de la tumeur primaire et le coût de la dispersion pour les cellules circulantes, et si ces coûts peuvent être modulés par l'apparement entre cellules. Il sera également nécessaire de considérer des hypothèses alternatives qui peuvent expliquer la métastase comme un processus adaptatif : notamment, l'émission de cellules tumorales circulantes pourrait participer à éparpiller les ressources du système immunitaire, diminuant ainsi la pression sur la tumeur primaire ; et la métastase pourrait simplement être adaptative pour les cellules qui colonisent de nouveaux substrats, et non pas pour la tumeur d'origine. Il est à noter que ces hypothèses ne sont pas mutuellement exclusives, et que le régime de sélection sur le processus métastatique pourrait varier au cours de la progression cancéreuse.

## 12.2 Le cancer dans le phénotype : une évolution à plusieurs échelles

Le cancer est un cas à part parmi les objets biologiques étudiés dans les sciences de l'évolution. Il s'agit d'une entité biologique, en conflit évolutif avec l'organisme, qui modifie son phénotype, et contre lequel les organismes développent de nombreuses adaptations. Pour autant, cette entité dérive de chaque organisme, et chaque cancer émerge de manière indépendante d'un organisme à l'autre : il ne devrait donc pas être possible de distinguer le cancer de l'organisme dont il est issu. Considérer le cancer comme une partie intégrante du phénotype pourrait offrir de nouvelles perspectives sur l'évolution de nombreux caractères.

En effet, le cancer est considéré comme inhérent à la multicellularité. Il est à la fois le résultat de caractères hérités d'ancêtres unicellulaires (c'est à dire une contrainte phylogénétique), et une conséquence de l'instabilité relative du mode de vie multicellulaire (c'est à dire un sous-produit, S J Gould and Lewon-

tin 1979). En ce sens, la multicellularité est stable dans le temps si et seulement si des mécanismes de contrôle du cancer sont sélectionnés, de sorte que les coûts du cancer sur la valeur sélective individuelle restent en deçà des bénéfices de la multicellularité. Il est donc parfaitement possible que ce caractère ait émergé de nombreuses fois au cours de l'histoire du vivant, mais n'ait pas pu persister durablement dans les contextes écologiques qui augmentaient le coût des mécanismes de suppression du cancer. De même, il est possible que ces mêmes contextes écologiques aient précipité le retour à l'état unicellulaire permanent dans certaines lignées multicellulaires : notamment les levures chez les Eumycètes, et les Myxozoaires chez les Eumétazoaires.

Par ailleurs, le cancer est susceptible d'exapter de nombreux caractères structuraux et fonctionnels encodés dans le génome d'un organisme, qu'ils soient hérités d'ancêtres unicellulaires, qu'ils soient uniquement exprimés durant le développement, ou encore qu'ils aient un rôle physiologique chez l'organisme adulte. Ce risque d'exaptation pose des contraintes sur l'évolution des mécanismes de suppression du cancer, mais il pourrait en poser sur d'autres caractères encore. Notamment, le cancer est capable de détourner des voies de communication cellulaires pour manipuler des cellules saines, pour manipuler la physiologie de l'organisme, et peut-être même pour manipuler son comportement ; le tout favorisant sa propre prolifération au détriment de l'organisme (section 10). Par conséquent, si une pression de sélection extrinsèque favorise l'émergence d'un caractère donné dans une population, le cancer pourrait agir comme une pression de sélection intrinsèque, sa capacité d'exaptation augmentant les coûts de ce caractère pour l'organisme.

Une perspective de cette thèse serait donc de déterminer : quels sont les caractères sur lesquels le cancer peut représenter une pression de sélection négative ; et quels sont les contextes écologiques qui peuvent favoriser ou défavoriser l'évolution de caractères modulant l'initiation et la progression du cancer. Pour ce faire, une approche emboîtée sera nécessaire. Dans un premier temps, il faudra quantifier l'effet de plusieurs caractères sur l'écologie et l'évolution des cellules cancéreuses dans une communauté de cellules coopératives : ceux capables de diminuer le risque de cancer ou de limiter sa progression, et ceux que les cellules cancéreuses sont capables de détourner pour manipuler les cellules saines. Dans un second temps, il faudra quantifier les coûts et bénéfices de ces caractères sur l'organisme (c'est à dire sur l'ensemble des cellules), en relation avec l'environnement : notamment les coûts des mécanismes anti-cancer (p. ex. sénescence, renouvellement cellulaire limité), et les bénéfices des caractères exaptables par le cancer (p. ex. coordination cellulaire). Ces étapes peuvent être réalisées grâce à la production de lignées mutantes, en faisant varier le nombre de copie d'un gène. Il serait ainsi possible de quantifier comment des variations dans l'expression d'un caractère résultent en des variations dans la progression cancéreuse et/ou la valeur sélective de l'organisme. De sorte à simplifier l'analyse quantitative, il faudra préférentiellement sélectionner des gènes non pléiotropes, soumis au moins d'épistasie possible, et impliqués dans un déterminisme mendélien. Dans le cas de l'évolution de la multicellularité, il faudra notamment comparer la valeur sélective des cellules coopérantes, la valeur sélective des cellules non-coopérantes, et la valeur sélective des cellules cancéreuses. Ceci pourrait être réalisé en sélectionnant des gènes qui possèdent des orthologues dans des organismes uni- et multi-cellulaires phylogénétiquement proches : levures et Basidiomycètes, Diatomées et Phéophycées, Myxozoaires et Cnidaires...

### **12.3 De l'évolutivité de l'individu : comment l'évolution contraint l'évolution**

Les modèles d'évolution emboîtée ont été essentiellement employés dans le cas des interactions hôte-parasite, où ils rendent compte de l'impact de l'évolution intra-hôte sur la virulence et la transmission (Mideo, Alizon, and Day 2008). Néanmoins, hôtes et parasites interagissent et évoluent au même plan : des populations d'hôtes co-évoluent avec les populations de parasites. Pour autant, les parasites ne sont pas les seules entités concernées par cette influence réciproque des dynamiques éco-évolutives intra-

et inter-organisme. Les cellules cancéreuses évoluent au sein de l'organisme dont elles sont issues, et leur dynamique éco-évolutive influence l'évolution de nombreux caractères chez les organismes. Ces caractères eux-mêmes influencent la dynamique éco-évolutive des cellules cancéreuses (section 9). De manière générale, les modèles d'évolution emboîtée peuvent être appliqués à tout caractère du phénotype individuel qui (i) est plastique au cours de la vie de l'individu, (ii) et suit une dynamique éco-évolutive.

Plusieurs phénomènes biologiques intra-individuels pourraient remplir ces deux conditions. Notamment, l'évolution du système immunitaire adaptatif pourrait être étudiée grâce à un modèle d'évolution emboîtée. En effet, l'organisme génère une grande variabilité de lymphocytes par le biais des mécanismes de *recombinaison V(D)J*, d'*hypermutation somatique*, et de *variabilité jonctionnelle* ; les lymphocytes sélectionnés par des stimuli internes ou externes subissent une *expansion clonale*. L'évolutivité du système immunitaire adaptatif est un caractère sous sélection chez les organismes (Earl and Deem 2004) : il doit être suffisamment évolutif pour être efficace face aux infections, mais suffisamment peu évolutif pour limiter le risque d'auto-immunité. Le système immunitaire adaptatif a déjà été envisagé comme évoluant à l'intérieur de l'organisme (p. ex. Alizon 2009) et comme un caractère sous sélection dans les populations d'organismes (Cooper and Alder 2006), mais n'a jamais explicitement été envisagé comme un caractère dont l'évolutivité était sous sélection. De même, plusieurs indices tendent à montrer l'existence d'une valeur sélective cellulaire, qui aurait un rôle au cours du développement et de la sénescence (Courgeon, Konstantinides, and Desplan 2015; Merino, Levayer, and Moreno 2016; Merino, Rhiner, et al. 2015) : l'évolutivité des cellules souches également pourrait également être un caractère sous sélection. L'évolutivité de l'individu pourrait en fait être sous sélection pour de nombreux caractères, certains comme la cognition pouvant même suivre une évolution non-biologique.

Une perspective de cette thèse serait donc de développer un formalisme général pour l'évolution des caractères évolutifs, basé sur des modèles d'évolution emboîtée. Ce développement devra se baser sur : (i) une revue exhaustive des caractères dont l'évolutivité serait potentiellement sous sélection ; (ii) la détermination systématique des processus à l'origine de la variabilité, de la transmission, et de la sélection à l'intérieur de l'organisme ; et la mise en équation (iii) du lien entre évolutivité d'un caractère et valeur sélective d'un organisme (iv) et de la contrainte exercée par l'évolution des organismes sur l'évolution intra-organisme (paysage génomique et paysage adaptatif). Dans le cas du système immunitaire notamment, les paysages adaptatif et génomique pourraient correspondre respectivement à l'ensemble des antigènes rencontrés durant le développement, et à l'ensemble des génotypes possiblement engendrés par la recombinaison VDJ, l'hypermutation somatique et la variabilité jonctionnelle. Un tel formalisme appliqué au système immunitaire pourrait être validé en comparant ses prédictions à celles des modèles pré-existant, et aux profils immunitaires de différentes espèces vivant dans différents environnements.

## 13 Conclusion générale

L'espèce humaine a été confrontée au cancer tout au long de son histoire. De l'Antiquité à nos jours, les sciences médicales n'ont jamais failli à avancer dans le combat contre la maladie. Nous avons appris à détecter, à identifier, à décomposer, à recomposer, à soigner, à re-soigner et à re-re-soigner une tumeur. Nous n'avons jamais autant connu le cancer, nous n'avons jamais autant su prévenir le cancer, nous n'avons jamais autant su soigner le cancer : nous avons appris à vivre avec le cancer. Pour autant, 8.2 millions de morts humaines sont encore imputables au cancer, chaque année et partout dans le monde. Près de 15 millions de nouveaux cas se déclarent chaque année, dont presque la moitié concernent le poumon, le sein, le colon et la prostate ; autant qu'il y a 40 ans. Le cancer lui-même est devenu la première cause de mortalité dans nombre de pays développés (environ 30% des décès en France), et cette tendance n'est pas près de s'arrêter. D'ici à 2030, on estime que l'incidence devrait augmenter de 68%, soit jusqu'à 25 millions de nouveaux cas chaque année, la majorité de l'augmentation étant attribuée aux pays en développement.<sup>15</sup> Cette tendance est le résultat d'un ensemble de facteurs : le vieillissement de la population mondiale, l'amélioration des techniques de détection, l'éradication d'autres causes de mortalité, etc. Ce dernier point révèle tout de même que, contrairement à d'autres maladies, le combat des sciences médicales contre le cancer est loin d'être gagné. Ce n'est pas en 5000 ans d'oncologie que l'on défait un milliard d'années de vie commune.

A l'époque où Richard Nixon déclara la guerre au cancer, des biologistes de l'évolution l'embrassaient comme un objet d'étude. Ce faisant, ils participaient à concrétiser la parole de Theodosius Dobzhansky : *rien en biologie n'a de sens, si ce n'est à la lumière de l'évolution*.<sup>16</sup> Ce que les sciences médicales tentent de comprendre et d'éradiquer aujourd'hui n'est autre que le résultat de l'évolution passée et présente. Le cancer en particulier progresse en nous selon une dynamique éco-évolutive – la même dynamique qui a porté le cancer de nos ancêtres jusqu'à nous. Et c'est à partir des années 1990 que des médecins s'emparèrent des sciences de l'évolution pour tenter, encore et toujours, de comprendre et éradiquer la pathologie. La médecine évolutionniste réussira-t-elle à éradiquer le cancer ? Nul ne peut en être certain ; mais cette approche a déjà offert de belles avancées dans la compréhension des origines et de la dynamique de cette maladie. Une chose reste sûre : face à un ennemi aussi répandu et aussi envahissant, la guerre totale demandera la collaboration de toutes les disciplines.

Au sein du vivant, le cancer est finalement une pathologie aussi universelle que les infections virales : on retrouve ses manifestations chez les Archées, les Eubactéries et les Eucaryotes – chez des organismes uni- et pluricellulaires. Il se révèle sous de nombreuses formes : des individus tricheurs dans les communautés procaryotes, jusqu'aux métastases animales, en passant par de simples tumeurs envahissantes chez des algues et des champignons. Le cancer devrait finalement être aussi ancien que la cellule, car il n'est que la manifestation perpétuelle de la lente transition entre coopération et antagonisme. L'exploitation est le mode de vie de la cellule cancéreuse : capable simplement de cesser toute coopération avec sa communauté, elle peut aussi s'en émanciper pour décimer des espèces entières. Mais les cellules cancéreuses s'éteignent, répétant toujours le même écocide en tuant leur hôte. Qu'à cela ne tienne, le cancer est un grand *bricoleur*, et ré-émergera ailleurs.

L'observateur attentif retrouvera des patrons répétés dans l'organisation du vivant : les cellules sont des organismes, vivant et évoluant dans des écosystèmes, lesquels sont eux-mêmes des organismes, vivant et évoluant dans des écosystèmes. L'observateur curieux s'intéressera aux causes de cette répétition : la nature bégaye-t-elle ? Le chercheur, attentif et curieux, détricotera, patiemment et à l'aveugle, la création de l'*horloger aveugle*.

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<sup>15</sup>Données mondiales de Cancer Research UK, <http://www.cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer>

<sup>16</sup>*Nothing in Biology Makes Sense Except in the Light of Evolution*, T. Dobzhansky, 1973



## Partie VI

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## Partie VII

# Annexes

Les annexes comprennent :

- le matériel supplémentaire de l'article *Non-cell-autonomous effects yield lower clonal diversity in expanding tumors* (section 6)
- un article auquel l'auteur de cette thèse a participé en qualité de co-auteur (7<sup>ème</sup>/17)
- un article auquel l'auteur de cette thèse a participé en qualité de co-auteur (5<sup>ème</sup>/14)
- un article auquel l'auteur de cette thèse a participé en qualité de co-auteur (13<sup>ème</sup>/16)
- un article auquel l'auteur de cette thèse a participé en qualité de co-auteur (7<sup>ème</sup>/16)



## **A Annexe 1 : Matériel supplémentaire de l'article *Non-cell-autonomous effects yield lower clonal diversity in expanding tumors***

Cette section comprend le matériel supplémentaire (*supporting information*) cité dans l'article suivant :

**Titre :** *Non-cell-autonomous effects yield lower clonal diversity in expanding tumors.*

**Auteurs :** Tazio Tissot<sup>17</sup>, Frédéric Thomas<sup>18</sup>, Benjamin Roche<sup>18</sup>

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Supporting information for:

**Non-cell-autonomous effects yield lower clonal diversity in expanding tumors.**

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This section gathers complementary references supporting our model and parameters, as well as complementary analyses of the simulations and complementary information on the model architecture. Tables S1 and S2 respectively expose a nonexhaustive review of non-cell-autonomous (NCA) effects impacting growth rates in tumors, and the list of parameters that were chosen in our model. We performed sensitivity analysis on Simpson index and tumor growth rate by computing Partial Rank Correlation Coefficients, which are displayed in Tables S3 and S4. We performed univariate linear regressions on PRCC residuals for Simpson index as a function of tumor growth rate, which are displayed in Table S5. Figure S1 shows the impacts of NCA effects on clonal diversity measured as Shannon index. The predictions of the linear regressions displayed in Tab. S5 are showed with residuals in Figure S2. Figure S3 shows the impacts of NCA effects on Simpson index for a subset of the largest tumors of Fig. 2B. Texts S1 and S2 expose respectively a detailed description and a simplified algorithm for the model.

**Table S1: Examples of non-cell-autonomous effects impacting the growth of noncarrier clones**

Type of NCA effect	Mechanism	Impacted cells	Effect on growth	Type of tumor
<b>Release of growth factors</b>	Acidic Fibroblast Growth Factor	All	+	<i>In vivo</i> mixture of carcinoma cells <sup>9</sup>
	Prostaglandin E2	Cancer stem cells	+	Human bladder cancer xenograft <sup>10</sup>
	Interleukin 6	High wtEGFR cells	+	Glioblastoma multiforme <sup>11</sup>
	Wnt1	Basal $\Delta$ Hras cells	+	Mouse breast cancer model <sup>12</sup>
	Upd cytokines	Ras <sup>V12</sup> cells	+	Fruitfly eye-antennal disc cancer <sup>13</sup>
	Insulin-like Growth Factor II	All	+	Neuroendocrine pancreatic cancer cells <sup>14</sup>
<b>Release of miRNAs</b>	Cell-independently processed miRNAs	Nontumorigenic epithelial cells	+	Breast cancer <sup>15</sup>
<b>Secretion of metabolites</b>	Lactic acid, ATP-H <sup>+</sup> pump	All but resistant cells	-	Human breast cancer among others <sup>16-18</sup>
	Hyperlipidemia induced by Very Low-Density Lipoprotein secretion	All	+	Subcutaneous mouse tumor model including Bcr/Abl-transformed precursor B cells <sup>1</sup>
<b>Remodeling of the local ME</b>	Matrix Metalloproteinase 14	All	+	Zebrafish-melanoma xenograft <sup>2</sup>
	Vasculogenic mimicry	All	+	Human melanoma, mouse breast cancer model <sup>3,4</sup>
<b>Recruitment of stromal cells</b>	Endothelial cells recruited by Vascular Endothelial Growth Factor	All	+	Mouse pancreatic cancer <sup>5</sup>
	Various stromal cells recruited by Interleukin 6	All	+	Mouse breast cancer xenograft <sup>6</sup>
<b>Unknown</b>	Unknown	All	-	Mouse mammary cancer, subcutaneous rat tumor model <sup>7,8</sup>

**Table S2: Parameter values of the model**

Parameter	Value	80% Value	120% Value
$N_0$	10000 <sup>19</sup>		
$b_0 = d_0$	$5.10^{-3}$ <sup>6,20</sup>	$4.10^{-3}$	$6.10^{-3}$
$t_{max}$	300 <sup>21</sup>		
$N_{max}$	$30 N_0$ <sup>19</sup>		
$r_{max}$	$2 b_0 = 2 d_0$ <sup>20</sup>	$1.6 b_0 = 1.6 d_0$	$2.4 b_0 = 2.4 d_0$
$b_{max} = d_{max}$	$5 r_{max}$ <sup>20</sup>		
$\mu$	$1.10^{-4}$ <sup>21,22</sup>	$8.10^{-5}$	$1.2.10^{-4}$
$\sigma$	1	0.8	1.2
$\alpha_t N_0$	$3 N_0$	$2.4 N_0$	$3.6 N_0$

**Table S3: Sensitivity analysis of Simpson index**

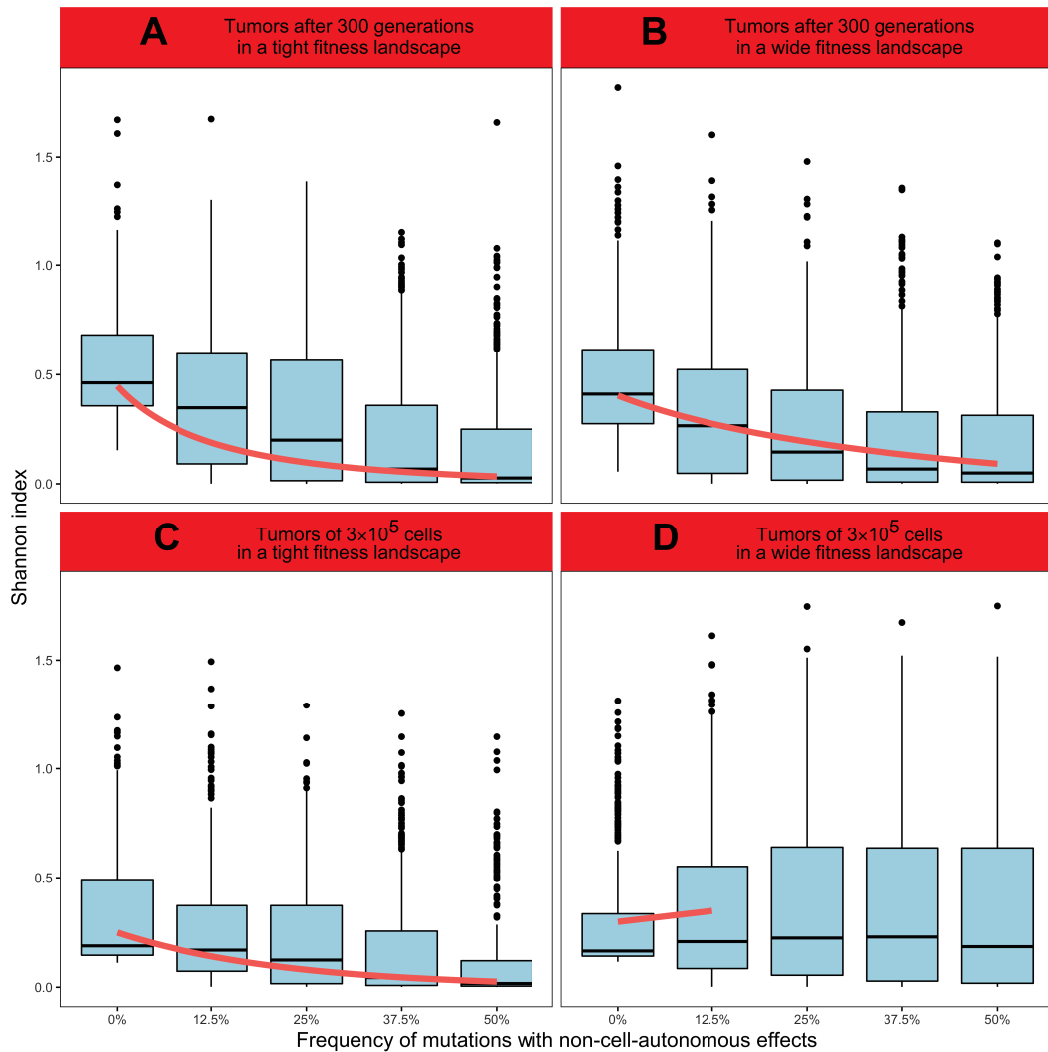
Variables		Minimal tumor size $\alpha_t N_0$	Basal division rate $b_0$	Variance of mutation effects $\sigma$	Range of mutation effects distribution $r_{max}/b_0$	Mutation rate $\mu$	Frequency of mutations with NCA effects
Tumors of same age Tight fitness landscape	PRCC	-0.051	$-6.7.10^{-4}$	-0.011	-0.059	-0.008	-0.431
	p	$1.1.10^{-2}$	$9.7.10^{-1}$	$6.0.10^{-1}$	$3.4.10^{-3}$	$7.0.10^{-1}$	$<2.2.10^{-16}$
Tumors of same age Wide fitness landscape	PRCC	-0.019	-0.009	-0.001	-0.041	0.012	-0.372
	p	$3.2.10^{-1}$	$6.4.10^{-1}$	$9.5.10^{-1}$	$4.2.10^{-2}$	$5.4.10^{-1}$	$<2.2.10^{-16}$
Tumors of same size Tight fitness landscape	PRCC	-0.004	-0.029	0.006	0.055	0.031	-0.388
	p	$8.4.10^{-1}$	$1.4.10^{-1}$	$7.5.10^{-1}$	$6.0.10^{-3}$	$1.2.10^{-1}$	$<2.2.10^{-16}$
Tumors of same size Wide fitness landscape	PRCC	0.002	0.043	-0.010	0.052	0.046	-0.057
	p	$9.0.10^{-1}$	$3.1.10^{-2}$	$6.2.10^{-1}$	$8.7.10^{-3}$	$2.1.10^{-2}$	$4.2.10^{-3}$

**Table S4: Sensitivity analysis of tumor growth rate**

Variables		Minimal tumor size $\alpha_t N_0$	Basal division rate $b_0$	Variance of mutation effects $\sigma$	Range of mutation effects distribution $r_{max}/b_0$	Mutation rate $\mu$	Frequency of mutations with NCA effects
Tumors of same age Tight fitness landscape	PRCC	0.278	0.178	0.003	0.376	-0.013	-0.221
	p	<2.2.10 <sup>-16</sup>	<2.2.10 <sup>-16</sup>	8.8.10 <sup>-1</sup>	<2.2.10 <sup>-16</sup>	5.1.10 <sup>-1</sup>	<2.2.10 <sup>-16</sup>
Tumors of same age Wide fitness landscape	PRCC	0.175	0.136	-1.9.10 <sup>-4</sup>	0.146	0.023	0.077
	p	<2.2.10 <sup>-16</sup>	7.4.10 <sup>-12</sup>	9.9.10 <sup>-1</sup>	2.3.10 <sup>-13</sup>	2.5.10 <sup>-1</sup>	1.1.10 <sup>-4</sup>
Tumors of same size Tight fitness landscape	PRCC	0.134	0.184	0.015	0.416	-0.007	-0.453
	p	2.1.10 <sup>-11</sup>	<2.2.10 <sup>-16</sup>	4.4.10 <sup>-1</sup>	<2.2.10 <sup>-16</sup>	7.1.10 <sup>-1</sup>	<2.2.10 <sup>-16</sup>
Tumors of same size Wide fitness landscape	PRCC	0.128	0.146	0.001	0.117	0.034	0.195
	p	1.5.10 <sup>-10</sup>	2.3.10 <sup>-13</sup>	9.6.10 <sup>-1</sup>	4.0.10 <sup>-9</sup>	8.8.10 <sup>-2</sup>	<2.2.10 <sup>-16</sup>

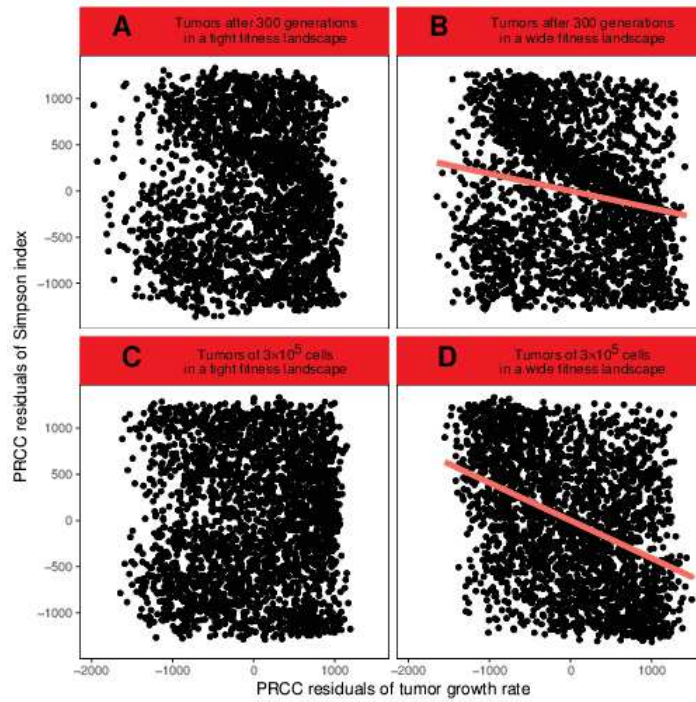
**Table S5: Univariate linear regressions for PRCC residuals of Simpson index as a function of PRCC residuals of tumor growth rate.**

PRCC residuals of Simpson index ~ PRCC residuals of tumor growth rate	Estimate	Standard error	Intercept	Standard error	R <sup>2</sup>
Tumors of same age – Wide fitness landscape	-1.861.10 <sup>-1</sup>	2.038.10 <sup>-2</sup>	1.105.10 <sup>-14</sup>	14.19	0.032
Tumors of same size – Wide fitness landscape	-4.082.10 <sup>-1</sup>	1.877.10 <sup>-2</sup>	-9.891.10 <sup>-14</sup>	13.20	0.159

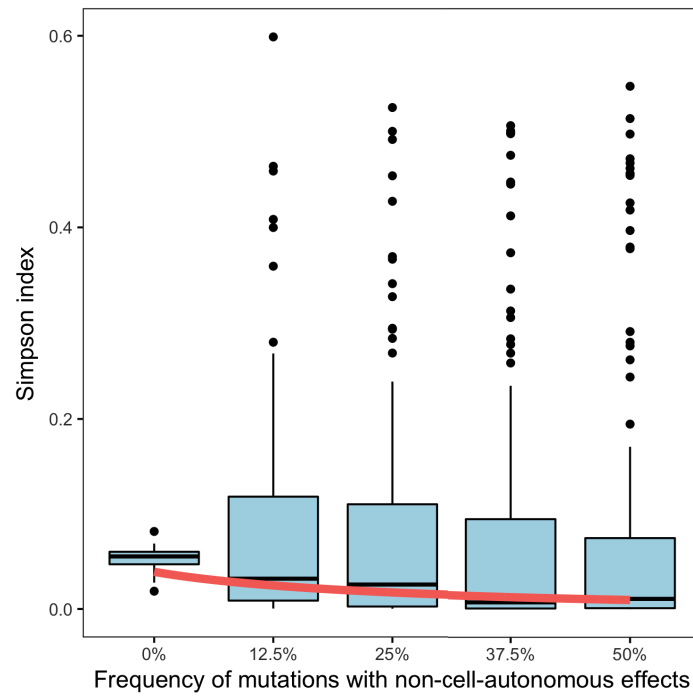


**Figure S1: Impacts of NCA effects on tumor diversification measured with Shannon index.**

Each panel displays the result of  $5 * 500 = 2500$  simulations. Shannon index is displayed in light blue, and linear regressions in red. (A) Simulations performed during 300 generations for a tight fitness landscape (linear regression,  $R^2=0.209$ ). (B) Simulations performed during 300 generations for a wide fitness landscape (linear regression,  $R^2=0.152$ ). (C) Simulations performed until the tumor reaches  $3 \cdot 10^5$  cells for a tight fitness landscape (linear regression,  $R^2=0.200$ ). (D) Simulations performed until the tumor reaches  $3 \cdot 10^5$  cells for a wide fitness landscape (linear regression,  $R^2=0.006$ ). Parameters used are displayed in Table S2.



**Figure S2: Relationship between clonal diversity and tumor growth kinetics.** Each panel displays the result of  $5 * 500 = 2500$  simulations. Residuals are displayed as black dots and the linear models built in Tab. S3 are displayed as red lines. (A) PRCC residuals of Simpson index as a function of PRCC residuals of tumor growth rate after 300 generations with a tight fitness landscape. (B) PRCC residuals of Simpson index as a function of PRCC residuals of tumor growth rate after 300 generations with a wide fitness landscape (linear regression,  $R^2=0.032$ ). (C) PRCC residuals of Simpson index as a function of PRCC residuals of tumor growth rate for  $3.10^5$  cells with a tight fitness landscape. (D) PRCC residuals of Simpson index as a function of PRCC residuals of tumor growth rate for  $3.10^5$  cells with a wide fitness landscape (linear regression,  $R^2=0.159$ ). Parameters used are displayed in Table S2.



**Figure S3: Impacts of non-cell-autonomous effects on clonal diversity for the largest tumors after 300 generations in a wide fitness landscape.** This figure is a subset of Fig. 2B (tumors after 300 generations in a wide fitness landscape), for tumors which size is greater than  $3 \cdot 10^5$  cells. This subset gathers 407 simulations: 22 for  $f_{NCA}=0\%$ , 65 for  $f_{NCA}=12.5\%$ , 98 for  $f_{NCA}=25\%$ , 107 for  $f_{NCA}=37.5\%$ , and 115 for  $f_{NCA}=50\%$ . Simpson index is displayed in blue, and a linear regression in red. This linear regression shows a significant negative association between the frequency of mutations with NCA effects and Simpson index (linear regression:  $\text{Log}(\text{Tumor growth rate}) = -2.24 \pm 0.62 \sqrt{f_{NCA}}$ ,  $t = -3.599$ ,  $p = 3.6 \cdot 10^{-4}$ ,  $R^2 = 0.029$ ).



## **Text S1: Model description**

### S1.1 Classes and methods

We consider only one class of individual cells, belonging to diverse clones, and upon which we apply events of division, mutation and death. The probability of division and death events are calculated by applying an exponential distribution on each rate:  $P = 1 - \exp(-rate \times \delta_t)$  where  $\delta_t$  is the model integration time step and *rate* is the individual rate expressed in the mean field approximation. The probability of mutation events is calculated by applying the exponential distribution on mutation rate  $\mu$ . Division, mutation and death events then occur stochastically according to the computed probabilities.

Each clone is associated to a vector (“mutationFitnessEffects”) which size corresponds to the number of clones having emerged during previous generations. This vector contains values corresponding to effects of mutations on every clone's growth (genetically encoded traits). We consider that mutations carried by a clone can have effects both on this clone's growth (i.e. CA effects) and on other clones' growth (i.e. NCA effects).

### S1.2 Program scheduler

Division, mutation and death events occur at discrete time, thereafter called “generations”. Two steps are generally considered at each generation. First, we determine the offset of each clone according to the number of divisions and deaths that have occurred for each clone during the time step. Then, when all clones have computed their next offset, their size is updated through a second function. This two-steps method is important to avoid synchronization issues.<sup>23</sup>

In our case, at each generation, a function “Step” is called for every cell for clones which size (“cloneSize”) is above zero. If a cell divides during this function, a clone attribute (“offsetCloneSize”) will be incremented of one unit. If a cell dies during this function, “offsetCloneSize” is decremented of one unit. If a cell mutates during this function, “offsetCloneSize” is decremented of one unit, and another clone attribute (“newMutations”) is incremented of one unit.

### S1.3 Division and death processes

Within the “Step” function, division, mutation and death processes take place (see Fig. 4). For each cell present in the system at this time step, a division rate and a death rate are computed thanks to basal rates ( $b_0$ ,  $d_0$ ) and mutations' fitness effects ( $r_{ij}$  with  $(i, j)$  in  $[1, n]$ ). For each individual, the division and death rates are computed as the basal division and death rates. The values of “mutationFitnessEffects” are tested whether positive or negative for each carrier clone present in the system (i.e. which size is strictly positive) during the generation: then, positive values are added to the division rate of the recipient individual, and negative values to its death rate. We limit the distribution of division and death rates in order not to obtain a superexponential growth;<sup>20</sup> thus we retain their computations between defined boundaries.

Then, for each clone  $i$ , the probabilities of division and death are computed with the previously computed division and death rates: the probability of division and death are equal to:

$$P_{division}^i = 1 - \exp(-(b_0 + \sum_j b_{ji}) \delta_t)$$
$$P_{death}^i = 1 - \exp(-(d_0 + \sum_j d_{ji}) \delta_t)$$

with  $b_{ji} = r_{ji}$  if  $r_{ji} \geq 0$  and  $d_{ji} = r_{ji}$  if  $r_{ji} < 0$ . Division and then death events are selected according to these probabilities. During each division event, mutation events are selected according to the probability  $P_{mutation}^i = 1 - \exp(-\mu \delta_t)$ .

After all cells have called the “Step” function, “cloneSize” is updated by adding to it the number contained in “offsetCloneSize”. Depending on “cloneSize” variations, we create new cells or destroy existing cells. If the updated “cloneSize” is below zero, it is raised to zero and the corresponding clone is then considered as extinct and no longer part of the tumor.

### S1.4 Mutations

For each clone, we select as many mutation events as there are units in “newMutations”. For each mutation event, we first create a new cell that we consider to be part of the descending clone (see fig. 1B). We then create a new vector “mutationEffects” based on the ancestral clone's vector: we draw its descending trait values in normal distributions centered on ancestral trait values, and bounded by two pre-determined limits. We also append all clone's vectors with a new trait value

drawn in normal distributions centered on the values of the effects on the ancestral clone. We also set boundaries to every distribution, still in order to maintain an exponential cell growth.

For each mutation event, there is a given probability (corresponding to 1 minus the pre-determined frequency of NCA effects) that the mutation has only CA effects, and no NCA effect. Then, we set to zero all the values of “mutationEffects” but the clone's effect on itself.

## Text S2: Model algorithms

### S2.1 Class model

```
VOID GO()
    BEGIN
        std::vector<Individual> ITableIndividual;
        FOR(int IIndex=0; IIndex<nbCellInit; IIndex++)
            Individual ITemp;
            ITemp.setClone(0);
            ITemp.setDivision(basalDivision);
            ITemp.setDeath(basalDeath);
            ITableIndividual.push_back(ITemp);
        END FOR
        abundanceClone.push_back(nbCellInit);
        mutantClone.push_back(0);
        offsetAbundanceClone.push_back(0);
        matrixEffect[0].push_back(0);
        double t=0;
        WHILE (t<tMax AND ITableIndividual.size(>)>0 AND ITableIndividual.size(<)<criticalSize)
            //For each cell, call step function
            FOR (Iint IIndexInd=0;IIndexInd<ITableIndividual.size();IIndexInd++)
                ITableIndividual[IIndexInd].step(t);
            END FOR
            //Update each clone size
```

```
FOR (int lIndex=0;lIndex<offsetAbundanceClone.size();lIndex++)
    //For each clone, creation of new cells if the demographic balance is positive
    IF (offsetAbundanceClone[lIndex]>0)
        FOR (int lIndexNew=0;lIndexNew<offsetAbundanceClone[lIndex];lIndexNew++)
            Individual lTemp;
            lTemp.setClone(lIndex);
            lTemp.setDivision(basalDivision);
            lTemp.setDeath(basalDeath);
            lTableIndividual.push_back(lTemp);
        END FOR
    END IF
    //For each clone, destruction of the first cells if the demographic balance is negative
    IF (offsetAbundanceClone[lIndex]<0)
        int lIndRemoved=0;
        int lIndexInd=0;
        WHILE (lIndexInd<lTableIndividual.size() AND lIndRemoved<(-offsetAbundanceClone[lIndex]))
            IF (lTableIndividual[lIndexInd].getClone()==lIndex)
                lTableIndividual.erase(lTableIndividual.begin()+lIndexInd);
                lIndRemoved++;
            ELSE
                lIndexInd++;
            END IF
        END WHILE
    END IF
```

```
END IF
abundanceClone[lIndex]+=offsetAbundanceClone[lIndex];
//Creation of new clones for mutant cells
double nbMutant=0;
int lIndexInd=0;
WHILE (nbMutant<mutantClone[lIndex])
    IF (ITableIndividual[lIndexInd].getClone()==lIndex)
        //Mutation event
        mutTrait.push_back(functionMutation(mutTrait[lIndex],lVariance,boundInf,boundSup));
        std::vector<double> lTemp;
        IF (randomUniform())<rateNCAMutation)
            FOR (int lIndexClone=0;lIndexClone<matrixEffect.size();lIndexClone++)
                lTemp.push_back(functionMutation(matrixEffect[lIndex][lIndexClone],lVariance,-1,1));
            END FOR
            matrixEffect.push_back(lTemp);
            FOR (int lIndexClone=0;lIndexClone<matrixEffect.size()-1;lIndexClone++)
                matrixEffect.push_back(functionMutation(matrixEffect[lIndexClone][lIndex],lVariance,-1,1));
            END FOR
            matrixEffect[matrixEffect.size()-1].push_back(functionMutation(matrixEffect[lIndex][lIndex],lVariance,-1,1));
        ELSE
            FOR (int lIndexClone=0;lIndexClone<matrixEffect.size();lIndexClone++)
                lTemp.push_back(0);
            END FOR
        END IF
    END IF
    nbMutant++;
    lIndexInd++;
END WHILE
```

```
matrixEffect.push_back(ITemp);
FOR (int lIndexClone=0;lIndexClone<matrixEffect.size();lIndexClone++)
    matrixEffect.push_back(0);
END FOR
matrixEffect[matrixEffect.size()-1][matrixEffect.size()-1]=functionMutation(matrixEffect[lIndex][lIndex],lVariance,-1,1);
END IF
abundanceClone.push_back(1);
abundanceClone[lIndex]=abundanceClone[lIndex]-1;
offsetAbundanceClone.push_back(0);
mutantClone.push_back(0);
lTableIndividual[lIndexInd].setClone(abundanceClone.size());
nbMutant++;
END IF
lIndexInd++
END WHILE
//Resetting the demographic balance and the number of mutants
offsetAbundanceClone[lIndex]=0;
mutantClone[lIndex]=0;
END FOR
//Incrementing time
t++;
END WHILE
END
```

```
DOUBLE FUNCTION MUTATION(DOUBLE valueToMutate, float lVariance, double boundInf, double boundSup)
```

```
  BEGIN
```

```
    double x1, x2;
```

```
    double finalValue;
```

```
    DO
```

```
      normalize(&x1,&x2);
```

```
      finalValue = x1*lVariance + valueToMutate;
```

```
    END DO WHILE (finalValue>boundSup OR finalValue<boundInf)
```

```
    RETURN finalValue;
```

```
  END
```

```
VOID NORMALIZE(double *x1, double *x2)
```

```
  BEGIN
```

```
    double W, V1, V2;
```

```
    DO
```

```
      double U1=randomUniform();
```

```
      double U2=randomUniform();
```

```
      V1=2*U1-1;
```

```
      V2=2*U2-1;
```

```
      W=V1*V1+V2*V2;
```

```
    END DO WHILE (W>1)
```

```
    double W_function=SQRT(-2*LOG(W)/W);
```



```
*x1=V1*W_function;  
*x2=V2*W_function;  
END
```

```
DOUBLE RANDOMUNIFORM()  
BEGIN  
RETURN rand()/(double)RAND_MAX;  
END
```

### S2.1 Class Individual

```
VOID INDIVIDUAL::STEP(float t)  
BEGIN  
float IProbaDivision=convertRateProbability(functionDivision(t));  
IF (IProbaDivision>randomUniform())  
offsetAbundanceClone[currentClone]++;  
float IMutationProb = 1-EXP(-mutationRate);  
IF (IMutationProb>randomUniform())  
mutationClone[currentClone]++;  
END IF  
END IF  
float IProbaDeath=convertRateProbability(functionDeath(t));  
IF (IProbaDeath>randomUniform())  
offsetAbundanceClone[currentSousPop]--;
```

```
        END IF  
    END
```

```
FLOAT INDIVIDUAL::FUNCTIONDIVISION(float t)
```

```
    BEGIN  
        float actualDivision=0;  
        actualDivision+=division;  
        int lIndex=0;  
        WHILE (actualDivision<divisionBound AND lIndex<abundanceClone.size())  
            double divisionTemp=mutTrait[lIndex]*matrixEffect[lIndex][currentClone];  
            IF (divisionTemp>0 AND abundanceClone[lIndex]>0)  
                actualDivision+=divisionTemp;  
            END IF  
            lIndex++;  
        END WHILE  
    END
```

```
FLOAT INDIVIDUAL::FUNCTIONDEATH(float t)
```

```
    BEGIN  
        float actualDeath=0;  
        actualDeath+=death;  
        int lIndex=0;  
        WHILE (actualDeath>deathBound AND lIndex<abundanceClone.size())
```

```
        double deathTemp=mutTrait[lIndex]*matrixEffect[lIndex][currentClone];
        IF (deathTemp<0 AND abundanceClone[lIndex]>0)
            actualDeath+=deathTemp;
        END IF
        lIndex++;
    END WHILE
END
```

```
VOID INDIVIDUAL::SETDIVISION(double pDivision)
```

```
    BEGIN
        division=pDivision;
    END
```

```
VOID INDIVIDUAL::SETDEATH(double pDeath)
```

```
    BEGIN
        death=pDeath;
    END
```

```
INDIVIDUAL::INDIVIDUAL(int pClone)
```

```
    BEGIN
        clone=pClone;
    END
```

```
INT INDIVIDUAL::GETCLONE()
```

```
    BEGIN
```

```
    RETURN clone;  
END
```

```
FLOAT INDIVIDUAL::CONVERTRATEPROBABILITY(double pRate)
```

```
    BEGIN  
        RETURN 1-EXP(-pRate);  
    END
```

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## **B Annexe 2 : Animal behaviour and cancer**

**Titre :** *Animal behaviour and cancer*

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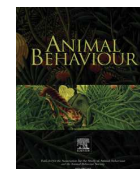
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## Essay

## Animal behaviour and cancer



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Scientists are increasingly coming to realize that oncogenic phenomena are both frequent and detrimental for animals, and must therefore be taken into account when studying the biology of wildlife species and ecosystem functioning. Here, we argue that several behaviours that are routine in an individual's life can be associated with cancer risks, or conversely prevent/cure malignancies and/or alleviate their detrimental consequences for fitness. Although such behaviours are theoretically expected to be targets for natural selection, little attention has been devoted to explore how they influence animal behaviour. This essay provides a summary of these issues as well as an overview of the possibilities offered by this research topic, including possible applications for cancer prevention and treatments in humans.

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Apart from being a leading cause of human death worldwide, cancer is primarily a pathology of multicellular organisms that has appeared during the transition to metazoan life, approximately 1 billion years ago (Aktipis & Nesse, 2013; Nunney, 2013). It is observed in nearly the entire animal kingdom, from cnidarians to whales (see Table 1; Leroi, Koufopanou, & Burt, 2003). Yet, oncology, as a scientific field, has until now developed in relative isolation from evolutionary and ecological sciences. This is unfortunate because links between these disciplines have the mutual

potential to reveal new perspectives and lines of research. For instance, while cancer is traditionally considered as a distinct pathology from a medical point of view, interdisciplinary approaches reveal that it is instead an unavoidable phenomenon governed by evolutionary principles and ecological relationships (Alfarouk, Ibrahim, Gatenby, & Brown, 2013; Casás-Selves & DeGregori, 2011; Daoust, Fahrig, Martin, & Thomas, 2013; Greaves, 2007; Merlo, Pepper, Reid, & Maley, 2006; Pepper, Scott Findlay, Kassen, Spencer, & Maley, 2009; Thomas et al., 2013). This is not a semantic problem, but rather a fundamental necessity to transform our understanding of cancer, its origin, the possible ways to control neoplastic progression and, probably most importantly, to prevent therapeutic failures (Aktipis & Nesse, 2013; Thomas et al., 2013). Similarly, although ecologists have ignored oncogenic phenomena, their roles in ecosystem functioning could in fact be important as

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<sup>1</sup> Equal contribution.



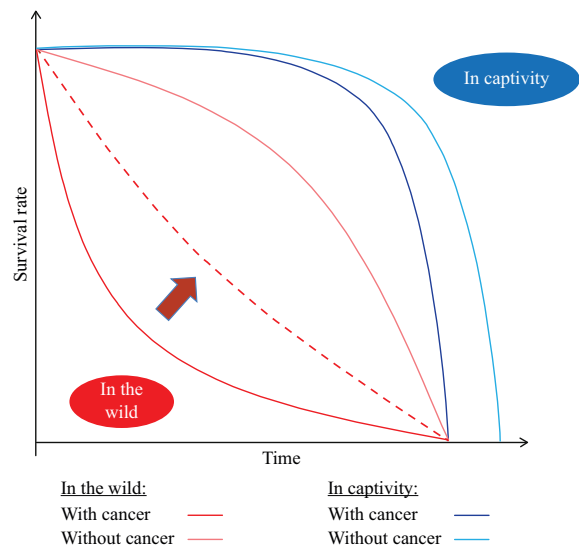
**Table 1**  
Examples of cancers observed in different metazoan groups and their known impacts on affected individuals

Group	Species		Context	Prevalence	Cancer	Factors favouring cancer	Impact	Source
	Common name	Latin name						
Invertebrates	Nonexistent	<i>Pelmatohydra robusta</i>	Laboratory population	Unknown	Undetermined	Genetic predisposition	Reduced population growth rate, reduced capacity of egg production	Domazet-Lošo et al., 2014
	Blue mussel	<i>Mytilus trossulus</i>	Cultured population	Up to 40% in northeast Pacific	Haemic neoplasia	Unknown	Increased mortality	C. M. Ciocan, Moore, & Rotchell, 2006; C. Ciocan & Sunila, 2005
Fishes	Drosophila	<i>Drosophila melanogaster</i>	Laboratory population (Oregon-R strain)	19% in 5 weeks old males	Gut and testis tumours	Unknown	Unknown	Salomon & Jackson, 2008
	Thornback skate	<i>Raja clavata</i>	Free-living	Unknown	Various forms, mainly affecting the skin	Unknown	Unknown	Ostrander, Cheng, Wolf, & Wolfe, 2004
	Coral trout	<i>Plectropomus leopardus</i>	Free-living	15% in part of the Great Barrier Reef	Melanomas	Genetic predisposition potentially associated with hybridization with another <i>Plectropomus</i> species.	Unknown	Sweet et al., 2012
	Brown bullhead	<i>Ameiurus nebulosus</i>	Free-living	Up to 68% in polluted North American rivers	Liver and skin tumours	Pollution (high concentrations of polynuclear aromatic hydrocarbons)	Damaged barbels	Baumann, Smith, & Parland, 1987; Pinkney, Harshbarger, May, & Melancon, 2001
Amphibians	Northern leopard frog	<i>Rana pipiens</i>	Free-living	Up to 6% in Minnesota populations studied between 1966 and 1977	Renal adenocarcinoma	Herpes virus infection	Probably causes death when metastasis occurs	McKinnell & Carlson, 1997; McKinnell, Gorham, Martin, & Schaad, 1979
	African clawed frog	<i>Xenopus laevis</i>	Laboratory population	5% in the studied population	Various forms the most common being hepatomas	Unknown	In some cases diseased individuals stop feeding and die	Balls, 1962; Goyos & Robert, 2009
	Montseny brook newt	<i>Calotriton arnoldi</i>	Free-living	Up to 27% in the remaining populations of Catalonia	Skin tumours	Potential role of UV-B radiations and elevated temperature to be confirmed	Unknown	Martínez-Silvestre, Amat, Bargalló, & Carranza, 2011
Reptiles	Green turtle	<i>Chelonia mydas</i>	Free-living	Up to 58% in the Hawaiian archipelago	Tumours of the skin, flippers, periocular tissues, carapace and plastron; nodules can also be found in all internal organs	Herpes virus infection	High mortality rates, impaired movements. Tumour-bearing turtles have a higher frequency of longer submergence intervals at night	Brill et al., 1995; Chaloupka, Balazs, & Work, 2009
	Egyptian mastigure	<i>Uromastix aegyptius</i>	Captive (zoo)	53% in the studied population	Multicentric lymphomas	Unknown	High mortality rate	Gyimesi et al., 2005
	Corn snake	<i>Pantherophis guttatus</i>	Captive (zoo)	12% in the studied snake population including 5 cases in corn snakes (the total number of corn snakes kept in the zoo is not indicated)	Neoplasms of the lymphoid and haematopoietic tissues are the most common	Unknown	Unknown	Catao-Dias & Nichols, 1999
Birds	Red-tailed hawk	<i>Buteo jamaicensis</i>	Both free-living and captive individuals	Unknown	Various forms	Unknown	Probably caused death in some of the reported cases	Forbes, Cooper, & Higgins, 2000
	Rock dove	<i>Columba livia</i>	Laboratory population	34% in the studied population	Various forms, the three most frequent cancers are seminomas, thyroid adenomas and lymphomas	Unknown	Probably caused death and/or infertility in some of the reported cases	Shimonohara, Holland, Lin, & Wigle, 2012

White-fronted goose	<i>Anser albifrons</i>	Free-living	23% of the shot individuals submitted to the laboratory	Multiple intramuscular mesenchymal tumours	Unknown	Unknown	Daoust, Wobeser, Raimie, & Leighton, 1991
Tasmanian devil	<i>Sarcophilus harrisi</i>	Free-living	Up to 80% in 2–3 year-old individuals	Tasmanian devil facial tumour disease	Transmissible cancer	High mortality rates	McCallum et al., 2007
Roe deer	<i>Capreolus capreolus</i>	Free-living	Up to 1% in central Europe	Skin tumours	Roe deer papillomavirus (CCPV1) infection	Tumours on the head may obstruct vision or affect the ability of the animal to feed	Erdélyi & Eatwell, 2012
Beluga	<i>Delphinapterus leucas</i>	Free-living	27% of the adults found dead in St Lawrence estuary	Various forms, most frequent cancers are adenocarcinoma of the intestine and stomach	Probable role of the polycyclic aromatic hydrocarbons found in beluga's prey	High mortality rates	Martineau et al., 2002

carcinogenesis influences individual competitive and dispersal abilities, susceptibility to pathogens and vulnerability to predation (Vittecoq et al., 2013). Despite recent progress towards greater convergence and dialogue between scientists working on oncology, ecology and evolutionary sciences much remains to be done to achieve full integration of these disciplines.

Here, we argue that a research direction that deserves to receive more attention concerns behavioural adaptations displayed by animals to prevent and/or to cure cancer with the ultimate aim of alleviating its fitness consequences. The main reasons why this topic has until now received little attention are twofold: it has traditionally been assumed that (1) cancer in wildlife is rare, and (2) behavioural adaptations against it are unlikely to evolve because fatal consequences of cancer usually occur late in life, when natural selection is weak. However, emerging evidence increasingly suggests that these two assumptions are wrong (Martineau et al., 2002; McAloose & Newton, 2009). First, similar to humans, oncogenic phenomena in animals are not restricted to (rare) metastatic cancers, but instead they include a large range of benign and malignant tumours that develop during the animal's lifetime and have various consequences for health and vigour (Vittecoq et al., 2013). Second, death resulting from cancer per se is likely to occur late in life only in laboratory conditions, not in the wild, because of interspecific interactions, especially predation and parasitism. Individuals displaying even a slight reduction in body condition will rapidly become preferential prey for predators or hosts for parasites (Thomas, Guégan, & Renaud, 2009). Therefore, we can conclude that predators and parasites can undoubtedly increase the detrimental consequences of oncogenic manifestations for survival in the wild (Fig. 1; Thomas, Guégan, & Renaud, 2009). Therefore cancer is likely to be an important indirect cause of early death for numerous animals, and natural selection is expected to favour adaptations that prevent cancer-induced reductions in vigour, all things being equal. Evolutionary pathways and genetic mechanisms against cancer are currently being extensively studied in



**Figure 1.** Cancer impact on survival: the importance of considering biotic interactions. The curves represent the survival rate of an individual according to whether or not it is cancerous and whether or not it is involved in a complex network of biotic interactions (i.e. in the wild). The red arrow and the dashed red line indicate how the survival curve of cancerous individuals can be shifted towards the curve of healthy ones thanks to anticancer behaviours.

some wildlife species (Caulin & Maley, 2011), but so far much less attention has been paid to behavioural adaptations.

The environmental factors potentially favouring cancer emergence and/or progression are potentially numerous, their origins being both anthropogenic (pollution in its many forms) and natural (e.g. natural radiation levels, oncogenic pathogens, transmissible cancers, secondary compounds of plants and various kinds of stress generally speaking). From this viewpoint, many behaviours may potentially contribute to reducing or increasing an individual's risk (and concomitantly consequences) of exposure. However, when the behaviour is both essential to the host's survival and reproduction and increases exposure to carcinogenic factors, the risky behaviour will be subjected to an evolutionary trade-off. Natural selection will most probably favour individuals whose behaviour ensures the best compromise between satisfying a need (e.g. reproduction) and minimizing the risk of detrimental consequences for health especially in iteroparous species. In addition, despite important differences between infectious diseases and cancers, tumour development can be closely compared to infections caused by foreign organisms since neoplasia broadly mimics their health consequences. Certain cancers are also directly transmissible (Murchison et al., 2014) and/or are induced by contagious pathogens (Zur Hausen, 2009). Therefore, based on these similarities, it is predicted that several of the behavioural adaptations that evolved in the context of host–parasite interactions should also be relevant in the context of cancer. The evolution of host–parasite interactions postulates that host species should be under selective pressures to first avoid the sources of the pathology, then prevent its progression if avoidance is unattainable, and finally alleviate the fitness costs if lethal development is not preventable. Here, we provide an overview of how similar adaptive responses against cancer in the wild contribute to shaping ecological functioning.

## PROPHYLACTIC BEHAVIOURS

### *Habitat Selection*

Life on earth has evolved under the ubiquitous presence of environmental natural mutagens including chemicals present in water, air and sediment such as polycyclic aromatic hydrocarbons (PAH) and various types of radiation including solar, gamma and charged-particle radiation. On a global scale, radiation from natural sources is a far more important contributor to radiation dose to living organisms than radiation from anthropogenic sources (Aarkrog, 1990). Health consequences for animals of natural variation in background radiation levels remain unknown, but are probably substantial since these variations have a significant effect on cancer-related mortality in humans (e.g. Brenner et al., 2003; Lubin & Boice, 1997; Anders Pape Møller & Mousseau, 2011; Prasad, Cole, & Hasse, 2004). Interestingly, Møller and Mousseau (2007) observed that birds prefer to breed in sites with low radioactivity in Chernobyl. Similarly, some fishes and aquatic invertebrates are able to avoid polluted habitats, which are of particular interest as some of the contaminants that are avoided are mutagenic (Da Luz, Ribeiro, & Sousa, 2004; De Lange, Sperber, & Peeters, 2006; Giattina & Garton, 1983). For instance, some freshwater invertebrates avoid sediments contaminated by PAH that have been shown to induce cancer in fishes and marine mammals. In addition to direct health costs, these examples could also represent the first evidence of habitat selection aimed at decreasing cancer burden in contaminated areas. Studying habitat selection behaviour in the context of cancer prophylaxis also implies that we consider the possibility of hormetic effects. Hormesis exists when a very low dose of a toxic agent (e.g. a mutagen) may trigger from an organism the opposite response to a high dose (Luckey, 2006).

Indeed some experimental studies suggest that a low dose of X-ray radiation may protect mice, *Mus musculus*, from the subsequent development of tumours (Yu et al., 2013). This model of dose response, however, remains debated at the moment (Costantini, Metcalfe, & Monaghan, 2010; Laviola & Macrì, 2013) and data are currently lacking to determine whether it may have impacts on adaptive responses against cancer in wildlife (see Møller & Mousseau, 2013).

### *Antioxidant Consumption*

Many cancers develop as a consequence of changes in DNA sequences. The evolution of efficient DNA repair of such changes in DNA sequences is likely to have been one of the most important evolutionary events following the evolution of multicellularity (Friedberg et al., 2006). The origin is double-strand DNA breakage. DNA repair is particularly important in the context of DNA damage caused by free radicals (Von Sonntag, 2006). Antioxidants including certain carotenoids play a key role in mopping up free radicals that otherwise damage DNA sequences (Møller et al., 2000), and animals show a strong preference for food containing antioxidants (Senar et al., 2010). The key role of antioxidants in sexual selection, life history and immunity may have an underappreciated relationship with prevention of the development of cancers.

### *Contagious Conspicific Avoidance*

Although the large majority of cancers are not contagious, there are at least two noticeable exceptions, namely the Tasmanian devil facial tumour disease (DFTD) and the canine transmissible venereal tumour (CTVT) (Murchison, 2008). Disease aetiology of these transmissible cancers follows similar pathways to those of sexually transmitted diseases, and does not comply with density-dependent selection forces. CTVT is transferred during sexual intercourse, while DFTD is transmitted via biting during social interactions, such as feeding and mating (Welsh, 2011). Transmissible cancers can be regarded as a novel type of (micro-) parasite, consisting of cells that are clonally derived from an original neoplasm in a long-dead host and are genetically distinct from their current host individual. Since both cancers impede fitness, by affecting sexual intercourse in dogs (CTVT) and reducing the survival of Tasmanian devils, *Sarcophilus harrisii*, to 6 months following infection (DFTD) (Murchison, 2008), evolutionary theory predicts that natural selection should favour susceptible individuals that are capable of recognizing infectious conspecifics and avoiding contagious contacts with them (Boots, Best, Miller, & White, 2009; O'Donnell, 1997). Predictions are not so simple, however, because while natural selection for less aggressive phenotypes should favour host survival, this could be counterbalanced by sexual selection, favouring traits (such as the extended and rough sexual intercourse of dogs and aggressive biting behaviour of devils) associated with increased mating and breeding success (Hamede, Bashford, McCallum, & Jones, 2009). More dominant (aggressive) males achieve higher rates of paternity and hence increased lifetime reproductive fitness in these species. In fact, dominant devils delivering bites, possibly on the tumours of other devils, are at higher risk of acquiring infection than submissive individuals receiving the bites (Hamede, McCallum, & Jones, 2013). Consequently, the behaviour of dogs and devils may actually have facilitated the emergence of clonally transmissible cancers by offering natural transmission routes for DFTD and CTVT (Murchison, 2008). Interestingly, although CTVT is the oldest and most widely disseminated cancer in the world (Murchison et al., 2014), its 11 000-year existence has not led to the evolution of less aggressive dogs, indicating the importance of sexual selection forces counterbalancing natural selection. Clearly, further research

on transmissible cancers is necessary before generalizations can be made on their potential to drive the evolution of prophylactic behaviours.

Pathogens, such as bacteria, parasites and viruses, are major initiators of oncogenesis in many, if not most cancers (Zur Hausen, 2009). When cancer-associated fitness consequences are significant, it is expected that, similar to other detrimental contagious pathogens, prophylactic behaviours should evolve to reduce the risk of infection by oncogenic pathogens as this is a front-line defence (e.g. Kavaliers, Choleris, Agmo, & Pfaff, 2004). Although the ecology of oncogenic pathogens in humans and wildlife is not completely understood, it seems that most of them are transmitted through close physical contact (Ewald, 2009). Avoidance of oncogenic pathogens should therefore preferentially affect behaviours requiring the close proximity and social interaction of notably sexual behaviours. Years of research on the influence of parasites on sexual selection have illustrated the many ways through which the detection and avoidance of infected individuals is possible in the animal kingdom (see David & Heeb, 2009). For cancer with external manifestation, the infectious status of a potential mate may be evaluated directly through perceptible signs of cancer. For example, green sea turtles, *Chelonia mydas*, are frequently affected by fibropapillomatosis (caused by a herpes virus), which is characterized by multiple external epithelial tumours that can be tolerated for years before death or recovery of the animal (Aguirre & Lutz, 2004). Detection could also rely on more subtle cues, especially when the transmission occurs from asymptomatic individuals. For instance, since both infections and cancers are often followed by a change in body odours (Prugnolle et al., 2009), potential mechanisms and abilities may have evolved to recognize and discriminate infected and uninfected individuals through body odours and to prevent contact between them, with the ultimate result of inhibiting infection by oncogenic pathogens. This is particularly expected given that olfactory cues have a prominent role in many animal species, providing an extraordinary amount of information on sex, social status, parasitic status and body condition (Kavaliers, Choleris, & Pfaff, 2005; Muller-Schwarze, 2006). Interestingly, experimental studies have shown that in mice, tumour-bearing individuals have a specific odour that can be detected by conspecifics (Alves, Vismari, Lazzarini, Merusse, & Palermo-Neto, 2010). However, host odour modifications may also correspond to pathogen adaptations aimed at favouring transmission (host manipulation, see for instance the cases of vector-borne pathogens: Lefevre & Thomas, 2008). This alternative possibility is important to consider in the context of oncogenic pathogens, because pathogens relying on intimate contact for their transmission are also expected to chemically manipulate or modify the attractiveness of their hosts to promote their own transmission (Prugnolle et al., 2009).

Compared with the abundance of ecological contexts that are associated with cancer risks, there remain few demonstrated examples of behavioural adjustments involved in cancer prevention. This is probably because few studies have embarked on this research pathway, but it may also be due to the costs associated with the modulation of behaviour: being choosy (with respect to habitat, food or partners) entails a cost that is higher when competition is more intense. In numerous situations, this cost probably cannot be offset by the benefit of avoiding cancer initiation unless the perception of cancer risk is reliable and the probability of developing an aggressive cancer is high. This last point leads us to consider the evolution of curative cancer behaviours as perhaps being more frequent than preventive ones, the perception of benign and malignant transformations by the host being more conceivable owing to the numerous internal (i.e. physiological, immunological) changes associated with carcinogenesis.

## POST CANCER EMERGENCE BEHAVIOURS

Because of fitness reductions associated with cancer progression, natural selection is likely to favour, when possible, behaviours that eliminate malignancies or slow down their progression and/or alleviate their fitness consequences.

### Self-medication

It is now well established that self-medication against parasites and pathogens is widespread in the animal kingdom (see De Roode, Lefevre, & Hunter, 2013; Huffman, 2001; Lozano, 1998). For instance, leaf ingestion among great apes helps them decrease their intestinal parasite load, especially when infected by nematodes (Huffman, 2001). It is theoretically expected that self-medication should also have evolved to suppress and/or control malignancies associated with fitness reductions, provided anticancer substances are available in the ecosystem. There is indeed a long list of food types, ranging from leaves and bark to fungi, with potential effective cancer treatment properties. Although examples are currently scarce, some species are known to occasionally consume plants containing antitumour compounds. Chimpanzees, *Pan troglodytes*, for instance, are known to self-medicate using different plants including some that have tumoral regression properties (Masi et al., 2012). Preference for antitumour foods may allow long-lived species and/or those living in habitats with high natural levels of mutagens to complement the purging effect of natural selection on oncogenes and further mitigate the impact of cancer on their health and fitness. More systematic studies of unusual feeding habits could help us understand such adaptations and identify the food items used to self-medicate, which could also contribute to the discovery of new anticancer drugs. It is also interesting to consider, as for any treatments targeting symptoms rather than sources, that self-medication against cancer would render selection 'myopic' to the genes responsible for the disease. Genetic mutations causing cancers might not be eliminated if self-medication can limit tumour development and concomitantly alleviate their fitness costs. The existence of self-medication could also help us to understand the persistence of oncogenic vulnerabilities in genomes.

### Sleep Duration and Immunity

The biological functions of sleep are not fully understood, but several studies support the hypothesis that sleep duration is strongly associated with enhanced immune defence (Bryant, Trinder, & Curtis, 2004). For example, mammalian species that sleep for longer also have substantially reduced levels of parasitic infections (Preston, Capellini, McNamara, Barton, & Nunn, 2009). Given that one of the functions of the immune system is to recognize and eliminate altered cells including malignant ones (De Visser, Eichten, & Coussens, 2006), cancer resistance may have played a role in the evolution of sleep. Furthermore, the duration of the sleep/wakefulness cycle strongly influences the production of various hormones including melatonin, which is known to be an important antitumour agent (Blask, 2009). The influence of sleep duration on the amount of this hormone in the body could represent another way in which the evolution of cancer resistance and sleep might have been interconnected in vertebrates. At the moment, it is not known whether species that evolved longer sleep durations are better protected from cancer, nor whether the longer sleep duration has led to redundancies in other anticancer strategies. For instance, herbivorous elephants, *Loxodonta africana*, with constant foraging, sleep only 3 h a day but possess 20 copies of the tumour suppressor P53 gene (Belyi et al., 2010; Caulin & Maley, 2011). Although the increased number of P53 gene copies in

elephants compared with other mammals has been attributed to their elevated risk of cancer resulting from their body size, it is not impossible that these genetic and phenotypic traits (short sleep, body size, herbivory and tumour resistance) have coevolved not only in this, but also in other species. However, before generalizations can be made, further studies would be necessary to determine the links between species characteristics (ecology, size and metabolism), sleep duration and natural defences against cancer.

Furthermore, it is not well understood/known whether increasing sleep time at the individual level would result in reduced progression and elimination of malignancies. In pathogen infections, such protection seems significant, as illustrated by the fact that mammals sleeping more following an infection have an increased chance of recovery (e.g. Toth, Tolley, & Krueger, 1993), while conversely sleep deprivation has the opposite effect (e.g. Everson & Toth, 2000). However, to decipher the exact role of increased sleep as an anticancer strategy we need to keep in mind that reduced environmental awareness and behavioural quiescence could result in a trade-off by increasing risk of predation, and impairing competition for resources and reproductive opportunities (Preston et al., 2009). In conclusion, understanding the links between sleep and cancer is an exciting and promising research direction since human studies support the hypothesis of a close physiological link between these two points (Blask, 2009). Indeed, night workers who experience sleep deficiencies and disrupted circadian cycles are generally at higher risk of cancer (e.g. Schernhammer, Kroenke, Laden, & Hankinson, 2006; Viswanathan, Hankinson, & Schernhammer, 2007). Similarly, the development of tumours is increased in mice with experimentally perturbed circadian cycles (Filipski et al., 2002, 2004). Results concerning the impact of interindividual differences in average sleep duration are less conclusive, some underlying higher risks of cancer in short sleepers (e.g. Girschik, Heyworth, & Fritschi, 2013; Thompson et al., 2011) whereas others find no impact (e.g. Pinheiro, Schernhammer, Tworoger, & Michels, 2006). Yet in both animals and humans such studies are complex owing to the difficulty of accurately estimating sleep duration and quality (Blask, 2009).

#### *Trade-off Between Immune, Somatic and Behavioural Functions*

Not surprisingly, the relentless effort by the immune system to eliminate malignant cells could result in trade-offs with other somatic functions. Infectious disease studies have revealed that sick animals use complex ways to optimize the balance of energy allocated to fighting the disease and to other essential activities, such as reproduction (see Aubert, 1999 for a review). For example, sick individuals will rest as long as possible, but conserve energy to manage tasks that are essential to their fitness such as protecting their progeny from predators or harsh weather conditions. Similarly, individuals with early cancer could have evolved to adapt their behaviour to maximize both their survival through energy allocation to their immune system and their reproductive success via protection of progeny. For instance, individuals with cancer could invest less in partner choice but allocate substantial energy to parental care. Apart from individual energy allocation strategies, adaptive modification of social behaviours could also provide an alternative option to counteract the loss of resources invested in fighting malignant cell formation (Hennessy, Deak, & Schiml, 2014). As an example, members of a social group could invest less energy in cooperation while still benefiting from the protection of the group.

#### *Trade-off Between Anticancer Defences and Life History Traits*

As we have outlined above, the adjustments of behavioural traits (e.g. reproductive investment) to reduce the impact of

detrimental oncogenic phenomena on fitness can be plastic and can influence the actions and life history of not only individuals but also entire populations (see also Jones et al., 2008 for an example of a life history trait).

Disease is a life history problem because underlying trade-offs between reproduction and maintenance cannot all simultaneously be maximized. Thus individuals that maximize survival at the expense of reproduction will also have to invest heavily in anticancer defences. This should result in a higher frequency of tumours in more long-lived species reflecting this trade-off. Likewise, in species with high fecundity we should expect less investment in control of cell division and hence expect to find a higher age-corrected frequency of tumours. These life history reflections should also affect the risks that animals take, with individuals that take great risks when encountering a predator having a higher frequency of tumours and cancers than individuals that take few risks (Cooper & Blumstein, 2015). Finally, many species in the tropics mature at old age, reproduce at low rates and have an extended life span. Such life histories should also be accompanied by low rates of parasitism and predation and heavy investment in anti-parasite and antipredator behaviour.

The investigation of the evolution of such trade-offs between energy allocated to fight against early cancer and other activities could be an important future research pathway that will contribute significantly to our understanding of animal behaviour and the evolution of cancer.

#### **BEHAVIOURS THAT REDUCE CANCER RISK FOR THE PROGENY**

Natural selection should favour individuals displaying behavioural traits that protect themselves from cancer emergence and/or progression, but it should also favour individuals displaying parental behaviours that reduce cancer risks for offspring. For instance, after a certain age, preferring breeding habitats that are less contaminated by mutagens could have little or no impact on cancer-induced reduction in adult survival, but it could be crucial to the probability of the succeeding offspring developing malignancies that are more or less detrimental. Therefore, even results that would appear as negative (i.e. no link between habitat selection and cancer for choosy individuals) should be handled with caution, while keeping in mind that adaptive behaviour to cancer avoidance is a transgenerational process, which requires longitudinal and multidimensional investigation. Another indirect way to prevent offspring from risking developing cancer is through sexual selection. According to the 'good genes' hypothesis (Møller & Alatalo, 1999) healthy individuals will provide their progeny with a superior genetic background. In the context of oncogenic phenomena, tumour-bearing individuals may potentially transmit genetic vulnerability to cancer to their offspring, whereas noncancerous individuals may provide their offspring with efficient genetic defences against cancer. A direct benefit for offspring from avoiding partners with malignancies and/or genetic vulnerabilities to cancer is through the 'efficient parent hypothesis' (Hoelzer, 1989), which stipulates that individuals mating with sick conspecifics will acquire a mate unable to provide high-quality parental care, which will lower the survival of their offspring. The hypothesis can also be applied to individuals with no developing cancer, but showing strong antitumour defences, since allocating energy and resources against malignancies can also lead to reduction in vigour. Therefore, both cancer and defences against it can theoretically be associated with reduction in vigour and hence poor parental abilities. However, noticeable exceptions deserve to be mentioned. For example in male fish *Xiphophorus* spp. the disadvantage of bearing an oncogene that is associated with a very high risk of melanoma development is overcome by its strong positive

effect on male reproductive success, notably due to more aggressive behaviours (Fernandez & Bowser, 2010). Such pleiotropic effects illustrate the complex ways in which oncogenes can be involved in sexual selection.

## CONCLUDING REMARKS AND FUTURE DIRECTIONS

The influence of oncogenic phenomena on the ecology and evolution of animal species is becoming a central research topic for certain scientists and for others it will be an inescapable factor to consider, given that most, if not all, multicellular organisms are affected by tumours that are more or less detrimental during their life. Compared to the important effort invested in the study of animal cancers, relatively few studies have considered the ecological contexts in which they occur, and the associated evolutionary consequences. This is unfortunate as it compromises our understanding of many aspects related to both the evolution of this pathology itself and to its potential to shape animal behaviour. At the moment, more research linking malignancies and behaviour in a greater diversity of biological models and ecosystems is clearly needed to correctly assess the behavioural consequences of cancer among animals. Future studies should also determine whether evolutionary convergences exist. Do similar cancer types in different species result in the same behavioural responses? Exploring the idea that behaviour contributes in return to the evolutionary dynamics of cancers (e.g. persistence of oncogenes, virulence of transmissible cancers and/or oncogenic pathogens) is another exciting direction of research. Knowing that most, if not all, ecosystems on our planet are now polluted by mutagenic substances to a greater extent than ever before, it seems essential to improve our knowledge of the interactions between animal behaviour and anticancer strategies as a response to human activities.

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## C Annexe 3 : Evolutionary perspective of cancer

**Titre :** *Evolutionary perspective of cancer: myth, metaphors and reality*

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## PERSPECTIVE

**Evolutionary perspective of cancer: myth, metaphors, and reality**

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**Abstract**

The evolutionary perspective of cancer (which origins and dynamics result from evolutionary processes) has gained significant international recognition over the past decade and generated a wave of enthusiasm among researchers. In this context, several authors proposed that insights into evolutionary and adaptation dynamics of cancers can be gained by studying the evolutionary strategies of organisms. Although this reasoning is fundamentally correct, in our opinion, it contains a potential risk of excessive adaptationism, potentially leading to the suggestion of complex adaptations that are unlikely to evolve among cancerous cells. For example, the ability of recognizing related conspecifics and adjusting accordingly behaviors as in certain free-living species appears unlikely in cancer. Indeed, despite their rapid evolutionary rate, malignant cells are under selective pressures for their altered lifestyle for only few decades. In addition, even though cancer cells can theoretically display highly sophisticated adaptive responses, it would be crucial to determine the frequency of their occurrence in patients with cancer, before therapeutic applications can be considered. Scientists who try to explain oncogenesis will need in the future to critically evaluate the metaphorical comparison of selective processes affecting cancerous cells with those affecting organisms. This approach seems essential for the applications of evolutionary biology to understand the origin of cancers, with prophylactic and therapeutic applications.

**Introduction**

Following the pioneer works of Cairns (1975) and Nowell (1976), cancer is perceived as a phenomenon whose origins and dynamics result from evolutionary processes (Cairns 1975; Nowell 1976; Merlo et al. 2006; Greaves and Maley 2012; Thomas et al. 2013). Placing cancer in an evolutionary ecology landscape is not a semantic problem, but rather a necessity to understand the origins and progression of

cancer with the ultimate aim of developing ways to control neoplastic progression and, most importantly, to prevent cancer and improve therapy when cancer occurs (Aktipis and Nesse 2013; Thomas et al. 2013). Because cancer cells abort their altruistic behavior in favor of a selfish life history strategy (that may eventually involve clonal cooperation), their evolution becomes, at least partially, governed by the same rules that apply to any autonomous entity prioritizing to maximize its own individual fitness. Several

authors proposed that insights into evolutionary and adaptation dynamics of cancers can thus be gained by studying the evolutionary strategies of organisms (Deisboeck and Couzin 2009; Lambert et al. 2011; Ben-Jacob et al. 2012; Sprouffske et al. 2012; Korolev et al. 2014). Although this reasoning is fundamentally correct, in our opinion, it contains a potential risk of excessive adaptationism, potentially leading to the suggestion of complex adaptations that are unlikely to evolve among cancerous cells. Determining the limits of adaptation resulting from oncogenic selection (*sensu* Ewald and Swain Ewald 2013), and more generally the differences (as well as similarities) between cancer cell and organismal evolution, is fundamental to the applications of evolutionary biology to carcinogenesis and has direct implications for therapies designed to thwart cancer cell proliferation.

What are the primary differences between cancers and organisms, with regard to evolution and adaptation? First, cancer is an ancestral disease that probably developed almost immediately following the transition from unicellular to metazoan life, about one billion years ago (Domazet-Lošo and Tautz 2010), but each cancer must 'reinvent the wheel' because their evolutionary products die within the host. Malignant cells are, at the best, under selective pressures for their altered lifestyle for only few decades, and a few dozen or hundreds of cell generations, and even less when the cancer itself reduces the lifespan of its host; for example, only 45 generations of replication are required, in principle, to go from a single cell to the 35–40 trillion cells in the human body. In this context, despite the rapid evolution of malignant cells, not all adaptive responses observed in (rapidly) reproducing unicellular organisms exposed to natural selection over tens of thousands to millions of years can be applied to cancer cells with short life histories. For instance, it has been argued that relatedness within tumors should influence cell decision to migrate (metastasize) and/or to locally cooperate (Deisboeck and Couzin 2009; Taylor et al. 2013). Such behavioral responses indeed exist in some animal species and microbes (West et al. 2006) to reduce competition and/or to promote the fitness of related individuals (Kawata 1987; Le Galliard et al. 2003; Moore et al. 2006). However, these life history strategies are the result of Darwinian evolution occurring over thousands and/or millions of years, not over mere decades. Unless ancestral heritable traits acquired prior to multicellularity are reactivated in cancerous cells, it is very unlikely that malignant cells would be able to display adaptive responses necessitating the ability of recognizing related conspecifics and adopting accordingly behaviors that depends on the kin context. Additional examples arise from the multistep process of metastasis. Studies have been arguing that the production and dissemination of metastatic cells should be counter selected at the initiation and early stages of tumors due to

local resource availability (the selection should favor cells resistant to anoikis (programmed cell death) and contact inhibition, but with no migratory potential (Gatenby and Gillies 2008). At later stages when damage to the tumor accommodating organ significantly restricts resource availability, tumor cells with increased motility should have selective advantage (and higher fitness) despite the cost of most migrating cells dying without establishing a new colony (Merlo et al. 2006). However, recent studies challenge the traditional view of a late acquisition of metastatic potential and instead propose that tumor cells acquire the motile phenotype early in tumorigenesis (Eyles et al. 2010) as a result of selection favoring expansion of primary tumors. Pathologic cell mobility could indeed contribute significantly not only to metastasis but also to primary tumor growth (cancer self-seeding theory (Norton and Massagué 2006)), but the pathways to the self-seeding that the primary tumor will take depends on the cues and concomitant selective forces of tumor microenvironment. Welcoming nutrient rich or hostile-depleted primary tumor site will result in different outcomes (i) dislodging, then reattaching in/at the primary site, (ii) dislodging, circulation in blood stream then reattachment in/at the primary site, (iii) dislodging, circulation in blood stream then reattachment in a novel (metastatic) site (Norton and Massagué 2006).

Variability in temporal resource quality generating different selection pressures, and resulting in phenotypic divergence, including sympatric speciation, has been observed in numerous species (Ehlinger 1990; Spinks et al. 2000; Garant et al. 2005). However, in our mind, the relevance of these examples to cancer remains questionable because they involve adaptive context-dependent behaviors that result from long-term evolutionary processes, at least more than a few years or decades. The extent to which the context-dependent behaviors can be favored during oncogenic selection remains to be determined. Second, cancer cell evolution through oncogenic selection involves different mechanisms for the generation of genetic and phenotypic variability than organismal evolution: cancer cell lineages are asexual, they undergo very high rates of mutation often due to genomic instabilities, and the mutations and epimutations generated most commonly involve losses of gene functions and large alterations to gene dosages, rather than the small alterations to functions and dosages that appear to typify adaptive organismal evolution. Organismal adaptations often involve changes to cellular regulation that decrease cellular reproduction (e.g., through cell cycle arrest) and survival (e.g., through apoptosis) when such regulation increases the evolutionary fitness of the organism; selection during oncogenesis, however, typically favors abrogations of these regulatory adaptations (Ewald and Swain Ewald 2013).

Selection during oncogenesis is therefore commonly destructive of organismal adaptations. Because destructive mutations are more common than mutations that generate or improve sophisticated biological mechanisms, mutation-driven evolution of cancer is feasible over short periods of time. The genomic variability of cancer cells, which may be due to mutagenic microenvironments favoring deficiencies in DNA repair (Breivik 2011), is among the causes of both malignancy itself and failures of chemotherapy due to evolved resistance (Merlo et al. 2006). Given that most mutations are deleterious to cell survival or replication, especially high variability must by first principles reduce the probability, precision, and sustainability of adaptive evolution in the context of complex fits to the environment. A possible example could be the neovascularization in cancer which involves the evolution of structures that are similar to blood vessels but less effective at transport because of aberrant angioarchitecture (Nagy et al. 2010). Larger mutations, as expected under genomic instabilities, are also expected to be less likely to generate adaptive change (Orr 2005). Asexual reproduction will also prevent or delay the coincidence of adaptive gene combinations within individual cells and thus should, in theory, hinder or delay the evolution of adaptations that rely on epistatic effects (De Visser and Elena 2007). Cancer cell populations surmount such population-genetic challenges, in part, through their very large population sizes, which greatly increase the scope for rare, favored alterations and reduce the efficacy of drift.

Contagious cancers (Tasmanian devil facial tumor disease (DFTD) and canine transmissible venereal tumor (CTVT) (Morgia et al. 2006; Murchison 2009)) present unique exceptions to the expectation, based on these considerations, of reduced adaptive evolution in cancer cells. In such cancers, fitness is not restricted by the death of the host, and the transmission of these clonal cancer cell lineages ensures their survival even after the carrying animal succumbs to the disease. CTVT and DFTD are the two oldest naturally occurring cancer cell lines, appearing approximately 11 000 and 20 years ago, respectively (Hawkins et al. 2006; Murchison et al. 2014). The evolutionary history of these cancers has allowed the development, pursuance, and implementation of highly elaborate adaptive strategies that maintain reproductive potential in the hostile micro- (stroma) and macro- (host's genotype) environment of their canine and devil hosts.

Finally, even though cancer cells can theoretically display highly sophisticated adaptive responses, it would be crucial to determine the frequency of their occurrence in patients with cancer, before therapeutic applications can be considered.

The extent to which selection akin to Darwinian evolution occurs in tumors is an old debate (Tarin et al. 2005;

Scheel et al. 2007; Talmadge 2007); while it undoubtedly contributes to cancer development and progression (e.g., resistance to therapies), certain adaptive traits including the metastatic cascade could also be explained by phenotypic plasticity rather than selection (Scheel et al. 2007; Gatenby and Gillies 2008; Gatenby et al. 2011). Although the role of phenotypic plasticity in creating pathogenic cell motility is now a generally accepted and well-supported concept (Scheel et al. 2007; Gatenby and Gillies 2008; Gatenby et al. 2011), restrictively using Darwin's theories to explain metastasis would remain a misconception. Therefore, we think that it is important to add and emphasize the risk of excessive adaptationism applied to cancer evolution, and we hope to stimulate additional debate in this topic. Clearly, further work, especially theoretical models, based in population genetics, genomics, and the evolution of adaptation, is necessary to properly address this point.

The evolutionary perspective on cancer has gained significant international recognition over the past decade and, as all novel scientific paradigms, generated a wave of enthusiasm among researchers. The heightened interest is understandable as somatic cellular selection and evolution indeed offer an elegant adaptive explanation for carcinogenesis with its many manifestations (neovascularization, evasion of the immune system, metastasis, and resistance to therapies). However, scientists who try to explain oncogenesis will need to critically evaluate the metaphorical comparison of selective processes affecting cancerous cells with those affecting organisms—both similarities and differences need to be carefully considered. This approach seems essential for the applications of evolutionary biology to understand the origin of cancers, to control neoplastic progression, and to improve therapies.

### Competing interests

The authors declare no conflict of interest.

### Authors' contributions

AA, BU, BC, RAG, MV, PE, AC, FR, BR, and FT were involved in the drafting of the article. All the co-authors revised the content of the manuscript and approved this version for publication.

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## Data archiving statement

Not applicable.

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## **D Annexe 4 : Cancer and life-history traits**

**Titre :** *Cancer and life-history traits: lessons from host-parasite interactions*

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## REVIEW ARTICLE

## Cancer and life-history traits: lessons from host–parasite interactions

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## SUMMARY

Despite important differences between infectious diseases and cancers, tumour development (neoplasia) can nonetheless be closely compared to infectious disease because of the similarity of their effects on the body. On this basis, we predict that many of the life-history (LH) responses observed in the context of host–parasite interactions should also be relevant in the context of cancer. Parasites are thought to affect LH traits of their hosts because of strong selective pressures like direct and indirect mortality effects favouring, for example, early maturation and reproduction. Cancer can similarly also affect LH traits by imposing direct costs and/or indirectly by triggering plastic adjustments and evolutionary responses. Here, we discuss how and why a LH focus is a potentially productive but under-exploited research direction for cancer research, by focusing our attention on similarities between infectious disease and cancer with respect to their effects on LH traits and their evolution. We raise the possibility that LH adjustments can occur in response to cancer via maternal/paternal effects and that these changes can be heritable to (adaptively) modify the LH traits of their offspring. We conclude that LH adjustments can potentially influence the transgenerational persistence of inherited oncogenic mutations in populations.

Key words: Cancer, evolutionary ecology, life-history traits, parasites, plasticity.

## INTRODUCTION

Cancer, a leading cause of human death worldwide, occurs across phylogenetical lineages, suggesting that cancer may have been present throughout the evolutionary history of multicellular organisms (Merlo *et al.* 2006; Aktipis and Nesse, 2013; Nunnery, 2013). Despite the widespread existence of cancer in the animal kingdom, oncology and other sciences have until very recently developed in relative isolation.

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This is unfortunate given that links between these disciplines have the reciprocal potential to reveal new directions for research and perspectives as well as proposing new therapeutic solutions. For example, it is increasingly acknowledged that applying ecological and evolutionary theory to cancer allows researchers to improve techniques to control malignant progression and prevent therapeutic failures (Aktipis and Nesse, 2013; Thomas *et al.* 2013; Rozhok and DeGregori, 2015). In addition, considering the ecological contexts in which cancers occur in wildlife improves our understanding of the evolution of the pathology itself, as well as to its theoretical potential to shape organism traits (Kokko and Hochberg, 2015). Ecologists have also proposed that oncogenic

phenomena have important influences on shaping animal behaviour, life history and even ecosystem functioning (Vittecoq *et al.* 2013, 2015).

Here, we propose a research direction deserving of more attention concerning life-history (LH) responses displayed by animals in the face of cancer risks and/or malignant progression. The primary reasons this topic has until now been poorly investigated are because it is often assumed that: (i) cancer in wildlife is rare; and (ii) adaptive responses against cancer are unlikely to evolve because cancer is a post-reproductive disease (see Vittecoq *et al.* 2013). However, evidence increasingly indicates that cancer is in fact likely to be common in wildlife, and has been documented in a diverse array of taxa from invertebrates to large mammals (Table 1). Furthermore, cancer can increase the risk that animals die early in life due to predation or parasitism (Martineau *et al.* 2002; McAloose and Newton, 2009). For example, oncogenic phenomena in wildlife (as in humans) encompass a large range of more or less malignant tumours, ranging from benign neoplasms to metastatic malignancies that induce various consequences on health and vigour, such as early death and decreased reproductive potential (Table 1; see also Vittecoq *et al.* 2013). As a result of these negative effects, animals can become more susceptible to interspecific interactions (especially predation and parasitism) that result in death *prior* to the end of the reproductive period. Together, these observations suggest that natural selection should favour adaptations that prevent cancer-induced reductions in fitness, just as we would expect for any other infections (Thomas *et al.* 2009). Thus, we draw on the literature related to parasitism and its effects on LH traits to guide us towards profitable avenues for cancer research. Whereas proximate mechanisms guarding against cancer, such as lower somatic mutation rates and redundancy of tumour suppressor genes, are currently being extensively studied in some wildlife species (Caulin and Maley, 2011; Roche *et al.* 2012), thus far much less attention has been paid to other traits, such as LH adaptations.

#### *Infection and cancer in multicellular organisms*

Importantly, cancer cells not only act similarly to parasites by diverting energy and resources from other vital functions of the host, but also a substantial proportion of malignancies are caused by infections (ca. 20% of human cancers; Ewald and Swain Ewald, 2015). Thus, infections could contribute to cancer directly or indirectly. Direct initiation results from pathogens (particularly intracellular parasites) altering cellular regulatory mechanisms (e.g. apoptosis and cell-cycle arrest) and cell proliferation rates, and therefore breaking down cellular barriers that would otherwise prevent oncogenesis. Infection-induced inflammatory responses may also

result in increased mutation rates and compromised proliferation signals, and concomitantly indirectly initiate malignant transformations (reviewed in Ewald and Swain Ewald, 2012, 2013). Although protozoans (e.g. *Plasmodium falciparum*, Molyneux *et al.* 2012), bacteria (e.g. *Helicobacter pylori*, Mager 2006; Ewald and Swain Ewald, 2014) and trematodes (e.g. *Schistosoma haematobium*, Mostafa *et al.* 1999; Ewald and Swain Ewald, 2014) have all been shown to directly or indirectly cause malignancies, viruses are the most frequent sources of infection-induced cancers (reviewed by Ewald and Swain Ewald, 2015). While oncogenic pathogens and their induced malignancies are well documented in humans and domestic animals, they are less well recorded in undomesticated captive animals, and are largely undetected in nature. Ewald and Swain Ewald (2015) have proposed several explanations for why cancer is rarely found in natural populations: (1) although benign neoplasms occur pervasively in multicellular organisms they rarely transition to detectable malignant tumours; (2) reduced survival due to malignancy [as a direct (detrimental to health) or indirect (increased predation) consequence of cancer] hinders detectability; and (3) diagnostics and evaluation of malignancy are inconsistent across species. The full scope of infection-induced cancers is still not known for any multicellular species, but interestingly infection-induced cancers are known to occur at young ages (e.g. cervical cancer in humans).

Cancer, being induced by pathogens or acting analogously to parasites, or both, clearly has a major impact on host' LH traits. We next discuss cancer as selective force on host LH traits.

#### *Why should cancer influence LH traits?*

Cancer, both solid tumours and blood cancers, can be thought of as a developing species that behaves in a manner akin to parasites (Duesberg *et al.* 2011). As far as host LH traits are concerned, parasites likely play an important role in their evolution because they often impose important selective pressures on the host (Michalakis and Hochberg, 1994). Similarly, cancer cells depend on their hosts for sustenance, proliferating inside their bodies, exploiting them for energy and resources, and thereby impairing their health and fitness. Based on these similarities, it is predicted that several of the responses that have evolved in the context of host-parasite interactions should also be relevant in the context of cancer (Vittecoq *et al.* 2013). Evolutionary theory on host-parasite interactions postulates that host species should also be under selective pressures to avoid the source of the pathology in the first instance (e.g. Hart, 1994), then prevent its progression once infected, and finally alleviate the fitness costs if further development is not preventable (Thomas *et al.* 2009).

Table 1. Examples of cancers observed in different metazoan groups and their potential impacts on host LH traits (modified from Vittecoq *et al.* 2015).

Common name	Latin name	Context and prevalence	Cancer type	Factors favouring cancer	Potential impact on host LH traits	Reference
Invertebrate						
Hydra	<i>Pelmatohydra robusta</i>	Laboratory population, unknown	Undetermined	Genetic predisposition	Reduced population growth rate, reduced capacity of egg production. Tumour-bearing polyps have significantly reduced fitness	Domazet-Lošo <i>et al.</i> (2014)
Blue mussel	<i>Mytilus trossulus</i>	Cultured and wild populations, up to 40% in northeast Pacific	Haemic neoplasia	Unknown	Increased mortality. Haemocytes showing significantly less phagocytic capacity leading to reduced immune function and mortality	Ciocan <i>et al.</i> (2006); Ciocan and Sunila (2005); Galimany and Sunila (2008)
Soft-shell clam	<i>Mya arenaria</i>	East coast of North America, up to 100% in affected areas	Haemic neoplasia	Retrotransposon (Steamer)	Increased mortality. Haemocytes showing significantly less phagocytic capacity leading to reduced immune function and mortality	Metzger <i>et al.</i> (2015)
Common fruit fly	<i>Drosophila melanogaster</i>	Laboratory population, 19% in 5-week old males	Gut and testis tumours	Unknown	Altered egg production, females with cancer reach peak oviposition earlier than healthy females	Salomon and Jackson (2008)
Fish						
Yellow sea horse & weedy sea dragon	<i>Hippocampus kuda</i> & <i>Phyllopteryx taeniolatus</i>	Captive (zoo), 9 out of 172 syngnathids analysed, mostly adult males	Cardiac rhabdomyosarcoma, renal adenocarcinoma, renal adenoma, lymphomas, exocrine pancreatic carcinoma, intestinal carcinoma	Unknown	Cancer potentially impacts feeding and predator evasion, as well as might reduce reproductive output by primarily affecting males (male sea horses being the carers of eggs)	LePage <i>et al.</i> (2012)
Coral trout	<i>Plectropomus leopardus</i>	Free-living, 15% in part of the Great Barrier Reef	Melanomas	Genetic predisposition – potentially associated with hybridization with another <i>Plectropomus</i> species	Fish with cancer are potentially less active and feed less	Sweet <i>et al.</i> (2012)
Amphibians						
African clawed frog	<i>Xenopus laevis</i>	Laboratory population, 5% in the studied population	Various forms the most common being hepatomas, ovarian tumours and teratomas	Various, e.g. virus, bacterium ( <i>Mycobacterium marinum</i> )	In some cases diseased individuals stop feeding and die. Ovarian tumours might impair reproduction	Balls (1962); Goyos and Robert (2009); Hardwick and Philpott (2015)
Reptiles						
Green turtle	<i>Chelonia mydas</i>	Free-living, up to 58% in the Hawaiian archipelago	Tumours of the skin, flippers, periocular tissues, carapace and plastron; nodules can also be found in all internal organs	Herpes virus infection	High mortality rates, impaired movements. Rapidly growing tumours disrupt the turtle's biologic functions (swimming, diving), predator evasion and feeding	Brill <i>et al.</i> (1995); Chaloupka <i>et al.</i> (2009); Page-Karjian <i>et al.</i> (2014)



Table 1. (Cont.)

Common name	Latin name	Context and prevalence	Cancer type	Factors favouring cancer	Potential impact on host LH traits	Reference
Egyptian mastigure	<i>Uromastyx aegyptius</i>	Captive (zoo), 53% in the studied population	Multicentric lymphomas	Unknown	High mortality rate. Lymphomas impair feeding, increase parasite burden and cause organ failure	Gyimesi <i>et al.</i> (2005)
Birds						
Rock dove	<i>Columba livia</i>	Laboratory population, 34% in the studied population	Various forms, the three most frequent cancers are seminomas, thyroid adenomas and lymphomas	Unknown	Adenocarcinomas of the female reproductive tracts and seminomas of testicles might impair reproduction	Shimonojara <i>et al.</i> (2012)
Domestic chicken	<i>Gallus gallus</i>	Breeding stocks, tumour commonly causes $\geq 1\%$ – $2\%$ mortality of birds, with occasional losses of $\geq 20\%$	Lymphoid leucosis	Avian leucosis virus	Subclinical infection decreases egg production and quality, and hence reproduction	Dunn (2013)
Mammals						
Tasmanian devil	<i>Sarcophilus harrisii</i>	Free-living, up to 80% in 2–3 year-old individuals	Tasmanian DFTD	Low genetic variation	High mortality rates, tumours on head impair vision and feeding. DFTD spreads via social interactions, primarily during mating. High mortality rates at reproductive age caused shift in reproductive strategy to semelparous from iteroparous	McCallum <i>et al.</i> (2007)
Santa Catalina Island fox	<i>Urocyon littoralis catalinae</i>	Population living on Santa Catalina Island, 48.9% of dead foxes examined from 2001 to 2008, 52.2% randomly sampled live mature animals	Ceruminous gland dysplasia and hyperplasia	Indirectly caused by ear mite ( <i>Otodectes cynotis</i> ) infection	The gross proliferative lesions and invasive carcinomas infiltrating adjacent bones may impair hearing and hence the hunting ability of the animals	Vickers <i>et al.</i> (2015); Moriarty <i>et al.</i> (2015)
Beluga	<i>Delphinapterus leucas</i>	Free-living, 27% of the adults found dead in St. Lawrence estuary	Various forms, most frequent cancers are adenocarcinoma of the intestine and stomach. Ovarian cancers in females	Probable role of the polycyclic aromatic hydrocarbons found in beluga's prey	High mortality rates. Intestinal carcinomas alter nutrition absorption, ovarian tumours might impair reproduction	Martineau <i>et al.</i> (2002)
California sea lion	<i>Zalophus californianus</i>	Free-living, 18–25% of animals examined post-mortem	Genital tract carcinomas	Genotype, persistent organic pollutants and herpesvirus	Since the urogenital carcinoma affects sub-adult and adult animals of both sexes (cervix and vagina of females and the penis, prepuce and urethra of males) it could potentially alter reproduction and LH strategies of seals	Browning <i>et al.</i> (2015)

*Costs on LH traits*

Parasitic organisms exploit their host for resources that could otherwise be used for maintenance, growth and/or reproduction (Poulin, 2007; Schmid-Hempel, 2011). Direct costs resulting from this exploitation can cause inter-individual (or inter-population) variation in LH traits such as fecundity and survival (Thomas *et al.* 2000). At the same time, inter-individual differences in physiology and LH productivity may 'drive' or encourage consistent variation in behaviour (Biro and Stamps, 2008; Biro *et al.* 2014), and differences in behaviour can in turn affect the likelihood of encounter rates with parasites and transmission of them between one another (Boyer *et al.* 2010; Dunn *et al.* 2011; Bull *et al.* 2012; Seaman and Briffa, 2015). Thus, inter-individual (or inter-population) variation in LH traits could at the same time be both causes and consequences of parasitism. Additionally, direct modifications of the host's LH traits may also result from toxic products of the parasite's metabolism (Michalakis, 2009). Finally, the complex machinery constituting the immune system often incurs metabolic costs that indirectly generate modifications of the host's LH traits as a result of trade-offs (Sorci *et al.* 2009). The extent to which these trade-offs are manifest are likely to differ among individuals that differ in their energetic and productive capacities (van Noordwijk and de Jong, 1986; Reznick *et al.* 2000; Biro and Stamps, 2008).

In the context of malignancies, the time elapsing from the appearance of the first cancerous cells to the development of a metastatic cancer may vary from weeks to years, or even decades, depending on individuals and types of cancer. The shape of the relationship between health/fitness-related traits and tumour development is not precisely known for most species and most cancers (see Vittecoq *et al.* 2015). Nonetheless, individuals harbouring tumours are likely to be, sooner or later, in a worse condition than healthy individuals on average, even if individuals differ in their intrinsic energetic and LH capacities. Frequent symptoms of cancer are extreme tiredness (fatigue) or weight loss, resulting from cancer cells using up much of the body's energy supply, or releasing substances that modify the way the body derives energy from food (Wagner and Cella, 2004; Ryan *et al.* 2007). Although cancer-related fatigue is one of the most prevalent symptoms in cancer sufferers, the precise aetiology of this distressing and debilitating symptom remains poorly understood. Given that energy allocation relative to energy acquisition is at the heart of predictions for how competing LH traits might be affected by such energy 'drains' (van Noordwijk and de Jong, 1986), a research focus on energetics might thus be very informative for understanding LH responses to cancer.

*Plastic adjustments of LH traits*

Host LH traits can undergo flexible and adaptive responses to parasitism in order to compensate for the negative costs exerted by parasites on host fitness (Hochberg *et al.* 1992; Michalakis and Hochberg, 1994). For instance, hosts unable to resist infection by other means (e.g. immunological resistance, inducible defences or long-distance migration) are theoretically favoured by selection if they partly compensate the parasite-induced losses by reproducing earlier (Forbes, 1993) or if their behaviour impedes the transmission of the parasite in spatially structured contexts (Débarre *et al.* 2012). Infected individuals may, for instance, increase their reproductive activities before dying or being castrated by parasites (Minchella and Loverde, 1981; Sorci *et al.* 1996; Polak and Starmer, 1998; Adamo, 1999), or simply increase their fitness through kin selection-mediated effects (Débarre *et al.* 2012; Iritani and Iwasa, 2014). Among recent examples, Vézilier *et al.* 2015 demonstrated that female mosquitoes parasitized by *P. falciparum* begin laying their eggs two days earlier, thereby compensating the loss of fecundity due to their reduced lifespan. In the context of cancer, preliminary results (Arnal *et al.* unpublished data) suggest that females in *Drosophila* harbouring early stages of tumours tend to reach the peak of oviposition earlier than healthy females before concomitantly dying sooner. As compelling as these recent studies are, clearly additional studies of this kind are necessary before generalizations can be made.

*Parental 'programming' and inheritance of LH traits*

The influence of parental (non-genetic) effects on their offspring's phenotype is increasingly acknowledged as an important adaptive mechanism in animals (Mousseau *et al.* 2009; Wolf and Wade, 2009). There is a growing body of evidence indicating that parasitic exploitation of a host can lead to changes in the phenotype of the hosts' offspring, though the latter are not parasitized (reviewed by Poulin and Thomas, 2008). For instance, animals infected with harmful parasites often produce smaller offspring because parents cannot allocate sufficient energy to reproduction (e.g. Hakkarainen *et al.* 2007; Gallizzi *et al.* 2008). Additionally, paternal stress can affect offspring phenotype by altering sperm phenotype and affecting post-zygotic development and performance (Crean *et al.* 2012, 2013; Rando, 2012; Bromfield *et al.* 2014; Zajitschek *et al.* 2014). Several proximate mechanisms have been put forward to explain parental effects due to infections, most involving hormonal or other physiological pathways, as well as epigenetic phenomena, and ultimately leading to offspring that are pre-adapted to the parasites they are most

likely to encounter based on their parent's experience (Sorci and Clobert, 1995).

Are there consequences of having 'cancerous' parents? Given that most if not all individuals among metazoan species accumulate precancerous lesions and *in situ* tumours in many organs as they age (Folkman and Kalluri, 2004), this question is relevant to virtually all multicellular organisms. Few cancers are directly transmissible, so the risk of offspring contagion is often not applicable. However, because of the health consequences associated with tumorigenesis, parents with more or less advanced malignancies are likely to be affected in their ability to provide adequate resources/parental care to their offspring. To our knowledge this question has never been empirically addressed. As for parasites, deeper trans-generational effects probably exist, as suggested by several studies indicating that epigenetic modifications that influence cancer risk can be inherited through the germline across multiple generations (reviewed in Fleming *et al.* 2008). Similar to infections, cancer risk could be correlated within families across generations. This should presumably be the case in species with low dispersal, living in areas (naturally or artificially) contaminated by mutagenic substances, because both parents and offspring experience the same ecological contexts. Similarly, the same should apply to cancer caused by inherited oncogenic vulnerabilities. At the moment there is little evidence available on the consequences of having parents harbouring tumours and/or oncogenic mutations on offspring phenotype, in terms of costs and adaptive (non-genetic) transgenerational effects.

Although parent-to-offspring transmission of cancer cells may be uncommon, parent-to-offspring transmission of infections that induce cancer appear to be moderately common (Ewald and Swain Ewald, 2015). For example, in humans, T-lymphotropic virus type 1 (Coovadia *et al.* 2007) and potentially hepatitis B virus are transmissible to offspring in milk (but see Chen *et al.* 2013) and cause cancer in a substantial proportion of those offspring (Ewald and Swain Ewald, 2015). In captive wildlife, vertical transmission of simian T-lymphotropic viruses in apes (Parrish *et al.* 2004; d'Offay *et al.* 2007), feline immunodeficiency virus in cats (O'Neil *et al.* 1995) and mouse mammary tumour virus in mice (Bentvelzen *et al.* 1970) is known, but their occurrence in the wild requires further study.

#### *Evolutionary change in the host population*

Whenever there is a genetic basis to LH traits, or trade-offs between them, evolutionary change in the host population can occur in response to 'infection' by cancer just as it would with parasites. For instance, selection may favour early sexual maturity when the risk of future infection and mortality is

high. Indeed, snails from localities with a high prevalence of castrating trematodes become sexually mature earlier than conspecifics living in areas of low prevalence (Lafferty, 1993; Fredensborg and Poulin, 2006). One of the best examples of altered LH strategies in response to exposure to cancer involves the Tasmanian devils (*Sarcophilus harrisi*) and their transmissible cancer, the devil facial tumour disease (DFTD). Following the appearance of DFTD, devils have responded to the cancer-induced mortality by rapidly transitioning from a late maturing iteroparous (multiple reproductive cycles) to an early maturing semelparous (single breeding) reproductive strategy (Jones *et al.* 2008).

#### *Concluding remarks*

Is it justifiable to ignore LH traits when studying oncogenic phenomena? In the light of this discussion, we suggest that the answer is clearly no. Cancer can directly affect LH traits by imposing costs and/or indirectly by triggering plastic adjustments and evolutionary responses, just as parasites are well known to do. Reciprocally, these effects can potentially influence cancer risks, through the evolution of differential cancer vulnerabilities in populations (e.g. Kokko and Hochberg, 2015). For instance, BRCA1 and BRCA2 mutations are inherited and predispose women to breast and ovarian cancer, but even though carriers of these mutations have a reduced survival, they also have enhanced fertility (Easton *et al.* 1995; Smith *et al.* 2012). This result may indicate antagonistic pleiotropy (i.e. when one gene controls more than one trait, at least one of these traits is beneficial to the organism's fitness and at least one is detrimental to fitness). However, since the adaptive response by the host also favours the transmission of BRCA1 and BRCA2 to the next generations, this suggests that the existence of LH trait adjustments could influence the persistence of oncogenic mutations in certain populations. In addition, such adjustments would be, in our opinion, a potentially more parsimonious alternative to the antagonistic pleiotropy hypothesis classically invoked to explain why oncogenic mutations persist at a higher frequency than expected by the mutation-selection balance (e.g. Bodmer, 2006; Risch *et al.* 2006).

To understand the evolution of LH traits in a cancer context, one must consider the complete ecological context in which individuals developing tumours live. Unfortunately, there is only limited data to date, supporting the hypotheses we have outlined above (Table 1). Clearly more data and research, including on the assumptions of cancers potentially affecting fitness related traits, are needed to draw a more substantiated parallel between cancer and infectious diseases. Because one single method or model cannot thoroughly integrate all the complexity of

the processes we have discussed, researchers interested in these adaptive responses must engage in greater exchanges and collaborations involving scientists from different disciplines. Finally, we strongly encourage researchers to systematically explore the myriad of symptoms displayed by cancerous patients in order to discover those that could be LH trait responses, *vs* those that illustrate pathological costs without adaptive value.

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## **E Annexe 5 : Cancer: an emergent property of disturbed resource-rich environments?**

**Titre :** *Cancer: an emergent property of disturbed resource-rich environments? Ecology meets personalized medicine*

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## REVIEWS AND SYNTHESSES

**Cancer: an emergent property of disturbed resource-rich environments? Ecology meets personalized medicine**

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**Introduction**

Cancer, a disease of multicellular organisms, probably developed almost immediately following the transition from unicellular to metazoan life, about one billion years ago (Merlo et al. 2006; Aktipis and Nesse 2013; Nunney

**Abstract**

For an increasing number of biologists, cancer is viewed as a dynamic system governed by evolutionary and ecological principles. Throughout most of human history, cancer was an uncommon cause of death and it is generally accepted that common components of modern culture, including increased physiological stresses and caloric intake, favor cancer development. However, the precise mechanisms for this linkage are not well understood. Here, we examine the roles of ecological and physiological disturbances and resource availability on the emergence of cancer in multicellular organisms. We argue that proliferation of 'profiteering phenotypes' is often an emergent property of disturbed, resource-rich environments at all scales of biological organization. We review the evidence for this phenomenon, explore it within the context of malignancy, and discuss how this ecological framework may offer a theoretical background for novel strategies of cancer prevention. This work provides a compelling argument that the traditional separation between medicine and evolutionary ecology remains a fundamental limitation that needs to be overcome if complex processes, such as oncogenesis, are to be completely understood.

2013). The existence of multicellular organisms requires cooperation among cells so that the morphology and proliferation of each individual cell are controlled by instruction from the organism (Maynard-Smith and Szathmàry 1995). In other words, the Darwinian unit of selection is the whole organism and not individual cells. A major problem faced by any cooperative system (see West et al. 2007) is that they are vulnerable to exploitation by cheaters. Cheaters are individuals that have access to group benefits, but partially or completely withhold their fair share

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of contributions to those benefits (Buss 1987; Maynard-Smith and Szathmàry 1995; Michod 1999). Selfish traits emerge from natural selection acting at multiple levels as cheaters gain individual advantage over the cooperative group that they exploit. In multicellular organisms, cooperating somatic cells give up their own reproductive interests to better propagate their shared genetic material. In contrast, cancer cells develop a self-defined fitness function in which their proliferation is dependent solely on its fitness within the context of the local adaptive landscape. Conflict between multicellular tissues and single cancer cells is thus central to understanding the pathogenesis and evolution of cancer (Nunney 1999; Merlo et al. 2006; Greaves 2007; Pepper et al. 2009; Thomas et al. 2013). While cooperative systems can theoretically be ruined by cheaters that decrease group fitness, intraspecific cheating occurs at low frequencies in the wild (e.g., Gilbert et al. 2007 for microorganisms; Barron et al. 2001 and Hughes et al. 2008 for eusocial insects). This is largely because various mechanisms have evolved to prevent cheater individuals from exploiting/parasitizing the collective (Frank 1995; Gardner and West 2004). This is also the case with cancer, as initiation of tumors in multicellular organisms seems unavoidable while their progression to malignancy is most often prevented (Bissell and Hines 2011; Holly et al. 2013). For instance, most individuals (at least in humans) harbor precancerous lesions and *in situ* tumors in a variety of organs (e.g., prostate, lung, thyroid, breast, pancreas) (see for instance Rich 1935; Franssila and Harach 1985; Nielsen et al. 1987; Sakr et al. 1993; Folkman and Kalluri 2004; Manser et al. 2005; Bissell and Hines 2011), but they do not necessarily lead to the development of malignant cancers (Folkman and Kalluri 2004). Strong constraints on somatic evolution to suppress cancer have evolved along with multicellularity; individuals with unregulated cell division were at a selective disadvantage over those that were able to prevent uncontrolled cell proliferation (Casás-Selves and DeGregori 2011; Aktipis and Nesse 2013). This undoubtedly explains why complex organisms evolved many potent cancer suppression mechanisms (at least through the period of sexual maturity and reproduction, Campisi 2003). These include cell-intrinsic checks that prevent cells from becoming cancerous, to integral controls that suppress cancer by operating at the level of tissue organization (see Ewald 2009; Casás-Selves and DeGregori 2011). Considering the trillions of cells in the human body, the multitude of possible mutations that can or do occur and the ensuing genomic instability, we can conclude that our ability to restrain the aberrant growth and behavior of precancerous cells is extremely efficient (Bissell and Hines 2011).

Because of the deleterious effects of the unrestricted proliferation of cancer cells, cancers are analogous in many

ways to the evolutionary and ecological dynamics of invading entities that harm cooperative and/or structured systems. Understanding the ecological contexts that promote or restrain proliferations in normally robust systems may provide insights into comprehending why some neoplasms develop into lethal tumors while others remain indolent for decades (see for instance Crespi and Summers 2005). The proliferation of cheaters is a common property of disturbed, resource-rich environments at all levels of biological organization (e.g., population, community, ecosystem, human society, eusocial insects, social amoeba, and social bacteria). We review here the evidence for this phenomenon, provide detailed description of the underlying causes, and suggest a theoretical perspective/framework in relation to oncogenesis. Finally, we elaborate on how acknowledging the applicability of these principles to tumor formation could provide valuable insights into identifying common evolutionary routes for cancer dynamics and offer novel strategies for prevention.

## Resources, disturbances and proliferation of profiting phenotypes at different biological scales

### Ecosystems

The invasion of a new species into an established ecosystem is determined not only by the characteristics of the invaders, but also by the invasibility of the ecosystem itself, which depends on several biotic and abiotic characteristics (see Mack et al. 2000; Catford et al. 2012 for reviews). For plant communities, Davis et al. (2000) proposed a general hypothesis of invasibility based on fluctuating resource availability with communities becoming more susceptible to biological invasion whenever there is an increase in the amount of available resources. This theory rests on the simple assumption that an invading species can indeed proliferate only if it has access to resources and does not encounter intense competition from resident species. This assumption originates from the principle that competition intensity should be inversely correlated with the amount of unused resources (Davis et al. 1998). Several theoretical models and empirical studies support this hypothesis. For instance, increasing water supplies in soil indirectly enhances the susceptibility of herbaceous communities by invasive woody and herbaceous vegetation (Grime and Curtis 1976; Harrington 1991; Li and Wilson 1998; Davis et al. 1999). Conversely, imposed drought decreases the invasibility of the same communities (Davis et al. 1998). The role of ecological disturbances in Davis et al.'s theory is important but mostly interpreted through their effects on resource availability because in the context of plants, disturbances are likely to introduce additional resources into the community and/or lead to a decline in the global resource uptake due to mortality or debilitation of the resident species.

### Cooperative systems

Several nonmutually exclusive mechanisms have been shown to favor the evolution and maintenance of cooperation among individuals (West et al. 2007). In addition to reciprocal benefits, enforcement (e.g., punishment, policing, etc.) appears to be a key component in the maintenance of cooperative behaviors. Here, cooperation is encouraged through specific adaptations in the social environment that function to make defection costly. It is important to note that social enforcement mechanisms are dependent on specific environmental conditions to operate optimally; a disruption in the environmental homeostasis could lead to a reduction in the efficiency or even a breakdown of social enforcement. In the following sections, we will overview the impact of stochastic disturbances on social enforcement mechanisms at different biological scales and discuss how they may influence the spread of cheater phenotypes.

### Community

Cooperation between different species, defined here as mutually beneficial interspecific interactions, plays a central role in the functioning of all ecosystems (Ferriere et al. 2002). Indeed, every species on earth is involved directly or indirectly in one or several mutualistic associations (Bronstein et al. 2004), which are central to their survival and reproduction (e.g., pollination, seed dispersal, etc.) (Stachowicz 2001; Kremen et al. 2007). Such associations are dynamic at both ecological and evolutionary timescales; changes in biotic and abiotic conditions can lead to shifts from once-beneficial mutualistic exchanges to less beneficial or even detrimental antagonistic associations (i.e., cheating) (West et al. 2007).

It is becoming apparent that human impact on global ecosystems can rapidly alter the cost-benefit trade-offs associated with cooperation (Palmer et al. 2008), destabilizing existing mutualistic partnerships and promoting shifts toward antagonism (Johnson 2010). For example, repeated and prolonged drought episodes in Mediterranean forests have created environmental conditions that select against water-saving benefits conferred by leaf endophyte mutualists (Moricca and Ragazzi 2008). Beneficial endophytic leaf partners have been found to adopt growth patterns that allow them to aggressively colonize weakened, dry tree tissues, facilitating their ability to exploit hosts as water becomes limiting (Moricca and Ragazzi 2008). Another example is that of the impact of fertilizer use on the mutualistic associations between legumes and mycorrhizal fungi. Briefly, photosynthetic plants harness the solar energy of the sun to synthesize organic molecules from CO<sub>2</sub>, water, and minerals. Mycorrhizal symbiosis increases the fitness of plants liv-

ing in mineral-deficient soils because fungi provide plants with access to limiting soil minerals, and in return, the plant provides the mycorrhiza with organic carbon. Mounting evidence suggests that fertilizer use may be detrimental to the persistence of plant–mycorrhizal mutualisms (Johnson 2010): Enrichment with fertilizers decreases the nutrient limitation that makes mycorrhizal mutualists beneficial and can lead host plants to severely decrease or cease resource allocation to their partners. This has been predicted to shift the competitive balance among mycorrhiza, favoring the evolution of more aggressive, antagonistic genotypes under increasingly high nutrient conditions (Thrall et al. 2006). These examples highlight that, even in systems where policing mechanisms are not needed for the maintenance of cooperative strategies, stochastic disturbances and increased resource availability favor noncooperative strategies.

### Social organization/interaction

As expressed by Nowak (2006), ‘humans are the champions of cooperation’, as cooperative behaviors have formed the bedrock of human societies throughout the ages. As we are intimately aware, modern societies are extremely dependent on the cooperation between individuals, cities, states, and countries to function properly. Interestingly, this also holds for hunter-gatherers, who typically exploit dense networks of exchange relations and practice sophisticated forms of food-sharing, cooperative hunting, and collective warfare (Fehr and Fischbacher 2004; Nowak 2006). In addition to the genetic, physiological, and psychological factors that are thought to be involved in the evolution of cooperative behaviors in humans (reviewed in Bowles and Gintis 2003; Fehr and Fischbacher 2004; Nowak 2006), social sanctions (laws, religious codes of conduct, cultural norms, etc.) and their enforcement mechanisms (e.g., social pressure, religious persecution, policing, etc.) also appear to be crucial for their maintenance in highly structured societies (Bowles and Gintis 2003; Fehr and Fischbacher 2004). This allows higher levels of cooperation to evolve and stabilize among unrelated individuals and in large groups (see Melis and Semmann 2010 for review).

Stochastic disturbances, such as natural disasters (e.g., earthquakes, volcanic eruptions, tsunamis, hurricanes, epidemics, floods) and human-caused catastrophes (e.g., toxic spills, nuclear accidents, plane crashes), have been shown to significantly disrupt social order (increased incidences of looting, physical abuse, divorce, etc.) most likely by reducing the efficacy of enforcement mechanisms (Nel and Righarts 2008), thus giving meaning to the old adage ‘when the cat is away, the mice come out to play’. For instance, a recent study, utilizing a comprehensive data set encompassing 187 international political entities from 1950 to the

present, provided robust evidence that stochastic natural disasters significantly increased the risk of violent civic conflict in the short term and medium term (Nel and Righarts 2008). Interestingly, the relationship between the number of climate-related natural disasters experienced and the risk of violent civil conflict is curvilinear, tracing an inverted U, peaking at rare (1–2) and frequent (>5) disturbances. Furthermore, these effects are magnified in countries that have intermediate to high levels of inequality, mixed political regimes, and sluggish economic growth (Nel and Righarts 2008).

#### *Eusocial organization/interaction*

Social insects (e.g., ants, termites, bees, wasps) provide a classic example of extreme biological cooperation characterized by a well-developed reproductive division of labor between queens and workers within colonies. Although best known for cooperation, complex insect societies are also vulnerable to parasitic attack from reproductive workers. Indeed, while workers usually cannot mate nor lay fertilized eggs, in certain species, they have retained the capability of producing males from unfertilized eggs. This selfish reproduction among group members is called ‘social cancer’ and may lead to the death of the colony in interspecific context (Oldroyd 2002). The African honeybee *Apis mellifera scutellata* of South Africa provides a nice illustration of a lethal and highly contagious ‘social cancer’ due to self-replicating workers. Since 1990, a clone of *A.m. capensis* workers has been invading colonies of *A.m. scutellata* and parasitizing brood with their eggs, causing the host *A.m. scutellata* to raise yet more parasitizing workers (Martin et al. 2002). A cheater lineage has also been observed in the Japanese ant *Pristomyrmex punctatus* (Dobata and Tsuji 2009), a species characterized by asexual reproduction and lack of a division of labor. All females fulfill both reproduction and cooperative tasks in the colony. Cheaters lay more eggs and take little part in cooperative tasks. Greater availability of food is apparently a key variable explaining why cooperator phenotype adopts a cheater trajectory (Dobata and Tsuji 2009).

#### *Microorganisms*

Although most evidence comes from laboratory conditions, it is now well established that some microorganisms exhibit cooperative, altruistic, and exploitative behaviors that are analogous to those observed in higher eukaryotes (Crespi 2001; Velicer 2003; Wingreen and Levi 2006). For instance, fruiting body construction in the myxobacteria and eukaryotic slime molds, biofilm and quorum-sensing systems in bacteria illustrate such cooperative interactions (See Crespi 2001 for review). In bacteria, the effects of resources and disturbances on cooperation are complex, depending on the spatial and temporal structure of the environment

(MacLean and Gudelj 2006), and also because disturbance frequency and intensity may not have equivalent effects. It has been shown in the bacteria *Pseudomonas fluorescens* that intermediate disturbance frequencies favors the cooperative trait of biofilm formation (Brockhurst et al. 2007) because disturbances cause population bottlenecks, increasing relatedness among bacteria, thereby favoring cooperation. Interestingly, very high frequencies of disturbance cause population densities to fall below that required for cooperation to be beneficial, while very low frequencies of disturbance allow evolved cheats to accumulate. Several studies confirmed that resource supply is an important factor in the evolution of cooperation (Brockhurst et al. 2008), reducing the costs of cooperation. Therefore, the fitness of cooperators and by extension their frequency within the population increases with increasing resource supply. However, further studies would be necessary before generalizations can be made on the positive effects of resource abundance on cooperation in bacteria.

The *Dictyostelia* or social amoebas represent a unique form of multicellularity that has the particularity to be conditional. Indeed, under nutrient-rich habitats, these soil organisms are unicellular, but when food supply is depleted, cellular agglomerates of up to a million of amoebas are formed to generate a motile structure, called the ‘slug’, which responds to chemical gradients and can migrate to light and warmth, that is soil’s top layer (Schaap 2007). Then, the sequence ends in a process called culmination and the slug forms the fruiting body in which a proportion of cells are sacrificed to build the stalk and the remainder differentiate into resilient dormant spores (Schaap 2011). The transient multicellularity in amoebas is a response to starvation, which indirectly suggests that selfish forms are favored when resources are abundant.

#### **Cancer**

##### *Stressors, caloric intake, and cancer*

Anecdotal evidence of a link between stress and disease progression is quite common in the developed world (Glaser and Kiecolt-Glaser 2005; Chida et al. 2008). More recently, mounting epidemiological and clinical data (e.g., twofold increase in breast cancer risk in women following a divorce, separation or death of a spouse (Lillberg et al. 2003), increased risk of lung cancer in men associated with job instability and death of a spouse (Horne and Picard 1979)), in concert with studies elucidating the mechanisms involved in stress-initiated and stress-enhanced cancers have provided empirical evidence for a link between stress and cancer emergence (Glaser and Kiecolt-Glaser 2005; Antoni et al. 2006; Kemeny and Schedlowski 2007).

Once initiated via a stressor, the dynamics of cancer progression can be additionally affected by diet (i.e., caloric

intake; Hursting et al. 2009). High-fat and sugar diets not only contribute to cardiovascular diseases and diabetes, but also significantly exacerbate cancer proliferation (Hursting et al. 2009). Due to growing clinical evidence and recent experimental studies identifying potential biological signaling pathways involved, calorie restriction (CR) is being heralded as the most potent, broadly acting dietary regimen for suppressing the carcinogenesis process (Hursting et al. 2009). Although the proximate mechanisms involved in stressor initiation and resource enhancement of cancer are relatively well understood, the evolutionary underpinnings remain largely unexplored. Investigating the joint role of CR in aging and oncogenesis could provide some evolutionary explanations. As CR appears to slow aging processes in a range of animal species (Weindruch and Walford 1988; Chapman and Partridge 1996; Houthoofd et al. 2002), it has been proposed that the response to limited food supply could represent a generalized evolutionary adaptation, potentially a strategy to cope with periods of famine (Kirkwood and Shanley 2005). CR organisms increase investment in cellular maintenance functions over reproduction, which may increase survival with a concomitant reduced intrinsic rate of senescence and hence enhance fitness once nutritional resources are restored (Kirkwood and Shanley 2005). CR contributes to lifespan extension by affecting the same metabolic and physiological pathways (i.e., growth factors, anabolic hormones, inflammatory cytokines, and oxidative stress markers) involved in oncogenesis (Longo and Fontana 2010). Therefore, we propose that the two processes, aging and oncogenesis, could have joint evolutionary histories, and the role of CR in controlling malignant formation could be an evolutionary spin-off of the adaptation to food restriction.

**Theoretical exploration**

To illustrate our verbal arguments, we developed a simple mathematical model to examine how sporadic disturbances, on immune system efficiency and resource supply, can yield a significant increase of cancerous cell accumulation. We used the following framework:

$$\frac{dH}{dt} = -cH + dRH \left[ 1 - \frac{C + H}{K} \right] - \rho_s H$$

$$\frac{dC}{dt} = \epsilon H + bRC \left[ 1 - \frac{C + H}{K} \right] - \rho_c C - \theta C$$

$$\frac{dR}{dt} = -cHR - aCR + \sigma$$

Within this mathematical framework, we considered two populations of cells: healthy (H) and cancerous (C). Each population of cells dies at a rate  $\rho$ , which differs between

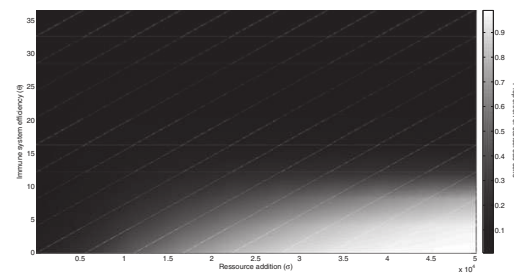
healthy and cancerous phenotypes, and uses the resources consumed to allow the creation of new cells at a rate  $d$  and  $b$ , respectively, while resources (R) are consumed by healthy and cancerous cells at rates  $c$  and  $a$ , respectively. Resources are added constantly through time at rate  $\sigma$ . We also assumed that the total number of cells cannot exceed a carrying capacity  $K$ , inducing then a competition between healthy and cancerous cells.

Cancerous cells arise at a rate  $\epsilon$  from the healthy cell population. However, population size of cancerous cells needs to reach some threshold to start an efficient proliferation. Indeed, a cancerous cell alone cannot propagate quickly and needs different factors (such as angiogenesis, see Hanahan and Weinberg 2011) to replicate. To mimic such fundamental requirement of tumor growth, we assumed that cancerous cells start consuming resources only when their population size reaches a given threshold. We thus assumed that  $b$  rate is driven by the following Gompertz function (a classic sigmoid relationship):

$$b = a_c e^{-b_c e^{-d_c R}}$$

where  $a_c$ ,  $b_c$ , and  $d_c$  are constant parameters shaping this threshold. Finally, cancerous cells are eliminated by immune system with rate  $\theta$ .

We first analyzed the influence of the combination of immune system efficiency and resource supply on the frequency of cancerous cells at the equilibrium without any sporadic disturbances. Figure 1 shows that both a decrease in immune system efficiency and an increase in resource supply are needed to reach high levels of cancerous cells.



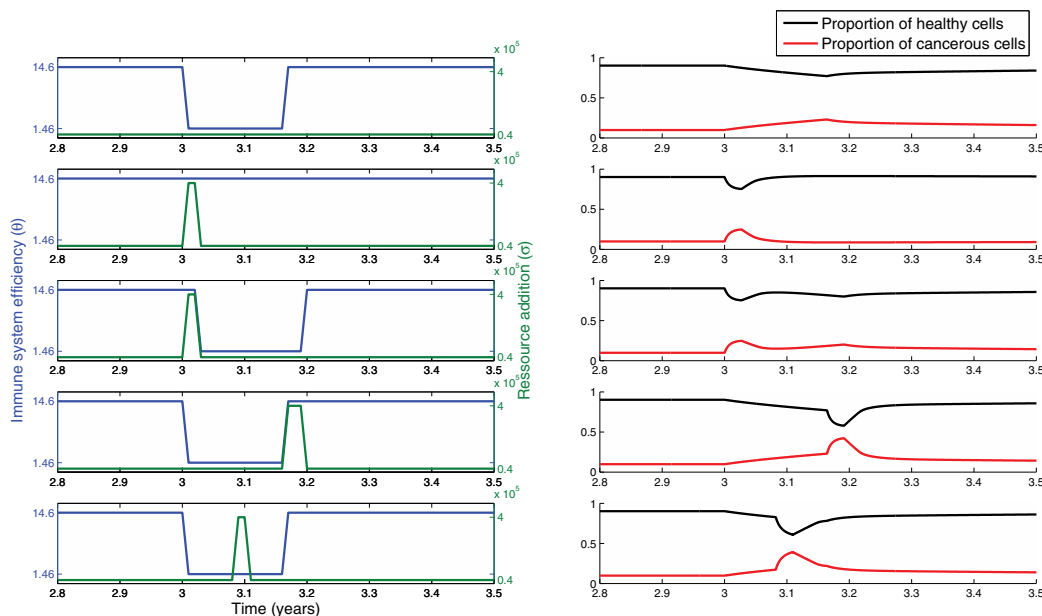
**Figure 1** Influence of immune system efficiency and resource supply on the appearance of cancerous cells. A decrease in y-axis represents a permanent diminution of immune system efficiency while an increase in x-axis represents a permanent addition in resources supply. Colors represent proportion of cancerous cells following a black to white gradient. Parameters:  $\epsilon = 365/1000 \text{ cell}^{-1} \text{ year}^{-1}$ ,  $K = 10^3$ ,  $\rho_s = 365/40 \text{ cell}^{-1} \text{ year}^{-1}$ ,  $\rho_c = 365/15 \text{ cell}^{-1} \text{ year}^{-1}$ ,  $a = 365 \text{ cell}^{-1} \text{ year}^{-1}$ ,  $c = 365/10 \text{ cell}^{-1} \text{ year}^{-1}$ ,  $d = 365/30 \text{ cell}^{-1} \text{ year}^{-1}$ ,  $a_c = 365/8 \text{ cell}^{-1} \text{ year}^{-1}$ ,  $b_c = 10^5$ ,  $d_c = 15$ .

Then, we tested the role of sporadic disturbances. Starting with an immune system efficiency and a level of resource supply that do not allow a high level of cancerous cells, we added sporadic disturbances on immune system efficiency (duration of 2 months, to mimic immunosuppression that could be observed during winter time) and resource input (duration of 10 days, to mimic a too rich diet for a special event like festive meals). Figure 2 shows that a burst of resources seems to play a larger role on the appearance of cancerous cells than immune system. This pattern is mainly driven by the higher production rate of cancerous cells compared with healthy ones, which allows cancerous cells to be more competitive and partly outcompete healthy cells temporarily following an additional resource supply.

These simulations also suggest that the timing of disturbances is an important predictor of sporadic accumulation of cancerous cells. The worst timing follows a disturbance on resource supply occurring during or after disturbance on immune system. As disturbance on resource supply has a larger impact than disturbance on immune system efficiency in our theoretical framework, immunosuppression allows an increase of cancerous cells frequency that is then

amplified by resource input. Nevertheless, because quantifying strength of immunosuppression or level of additional resource supply deserves a full study, we cannot conclude which process is the most important.

This initial theoretical approach aims at showing that each type of disturbance may have a different outcome on cancerous cell population dynamics. It also underlines the strong influence of the timing of such disturbances. The simplicity of this model does not allow studying the influence of these sporadic disturbances may have in the long term because more sophisticated processes should be then considered. For instance, reaching 50% of cancerous cells among the whole cell population (as our simulations show), even temporarily, definitely increases the probability of metastasis and jeopardizes prognosis of the individual. Indeed, such proportion is expected to break down the homeostasis of the organism considered, with important consequences on the individual health that we do not address here. While addressing these complex mechanisms goes over the edges of the current study, we believe that such theoretical framework should be extended and analyzed deeply.



**Figure 2** Profiles of disturbances (left) and consequences for cancerous cell population dynamics (right). (First line) Disturbance on immune system efficiency only. (Second line) Disturbance on resource supply only. (Third line) Disturbance on resource supply occurs before disturbance on immune system efficiency. (Fourth line) Disturbance on resource supply occurs after disturbance on immune system efficiency. (Fifth line) Disturbance on resource supply occurs during disturbance on immune system efficiency.  $\theta = 365/25 \text{ cell}^{-1} \text{ year}^{-1}$ ,  $\sigma = 4.10^4 \text{ year}^{-1}$ , other parameters are identical to those in Fig. 1.

### Implications for cancer prevention

The proliferation of profiteering phenotypes is often an emergent property of disturbed, resource-rich environments relevant at all scales of biological organization. Whether or not carcinogenesis, which can be viewed as the proliferation of profiteering/cheating cells, is also governed by this principle is a legitimate question. We argue that instead of being a distinct phenomenon, cancer is a particular manifestation of a quasi-universal ecological process that is the proliferation of profiteering phenotypes in disturbed systems with unused resources. Several studies have compared the metastatic cascade to biological invasions by exotic species (e.g., Gatenby et al. 2009; Chen and Pianta 2011). While this comparison is acceptable for several ecological and evolutionary reasons, we would like to extend the theory to the development of primary tumors.

Our concept aligns closely with the general theory of invasibility proposed for plant communities as described above (Davis et al. 2000; Mack et al. 2000). However, there is one fundamental difference: while disturbances directly act on the level of available resources in plant communities, the primary detrimental effect of disturbances in carcinogenesis is through the disruption of natural barriers against undesirable invasions (notably policing, e.g., immune system). By analogy with this ecological literature, two key conditions must be met for an invasive cancer to develop: (i) available resources for seeds to germinate, and (ii) damaged protective barriers unable to inhibit the proliferation/invasion. Analyzing in more detail how we could potentially act on these two conditions and/or their interactions may offer a theoretical background for novel strategies of cancer prevention.

### Presence of unused resources

Because weight gain leading to overweight occurs when energy intake chronically exceeds energy expenditure (Romieu et al. 1988), ponderosity (body weight relative to height) can be interpreted as a surrogate of unused resources. Our ancestors evolved from a nutritional landscape very different from today. This is especially true in westernized societies in which the diet is characterized by large amounts of high-calorie and high-fat food. Eating in the past also required high-energy investment which made it impossible for most people to accumulate much surplus as fat (Eaton and Konner 1985). This mismatch between ancestral conditions and current lifestyles results in several health problems, such as obesity, hypertension, diabetes, and cancers (Nesse et al. 2012). Numerous studies have successfully linked calorie intake and cancer and identified several of the mechanisms involved (e.g., hormones and growth factors, insulin, IGF-1, leptin, adiponectin, steroid

hormones, inflammation, sirtuins; see Hursting et al. 2009 for a review of the past 30 years of CR research). Calorie surplus leads to the presence of available resources and is therefore likely to favor invasive cancers that rely on the rapid cellular growth which itself depends on an increase in supply of energy and of substrates for the biosynthesis of all the macromolecules required to build new cells. In accordance with this hypothesis, the incidence of cancer is increasing in developing countries owing to changes in lifestyle and diet that occur with economic development (consumption of highly refined foods, sugars and/or saturated fat; Prentice and Sheppard 1990; Bergström et al. 2001; Bianchini et al. 2002; Rastogi et al. 2004). Cancer progression also likely depends on the energy balance (nutritional excess/lack of activity) and composition of diet rather than simple calorie intake (Holly et al. 2013). In accordance with the idea that the presence of unused resources favors the ability of seeds to germinate, not the quantity *per se*, an interesting parallel could be made to countries where rapidly changing lifestyles resulted in diet having a more significant effect on the progression of cancers to clinical stages than on the initiation of latent cancers (Shiraishi et al. 1994; Holly et al. 2013). Theoretically, natural selection could eventually fix these oncogenic disorders (as well as other calorie associated conditions), but hundreds or thousands of generations would be required, and the selection pressure would only have influence on cancers occurring through the period of sexual maturity and reproduction. An efficient solution to reduce the risks of cancer progression and metastasis would be to adopt a low-calorie diet. During high-caloric restriction, to ensure cellular survival, autophagy, a catabolic mechanism, degrades unnecessary or dysfunctional cellular components. The contributing role of autophagy in the context of CR-induced health benefits has been recently unraveled (Pallauf and Rimbach 2013). Genetic inhibition of autophagy induces degenerative changes in mammalian tissues that resemble those associated with aging, and normal and pathological aging are often associated with a reduced autophagic potential. Pharmacological or genetic manipulations that increase lifespan in model organisms often stimulate autophagy, and its inhibition compromises the longevity-promoting effects of caloric restriction, activation of the deacetylase sirtuin 1, inhibition of insulin/insulin growth factor signaling, or the administration of rapamycin, resveratrol, or spermidine (Steeves et al. 2010; Rubinsztein et al. 2011). However, this solution is difficult to accept for many people, presumably because we also have been selected to appreciate sweet and fatty foods (Nesse et al. 2012). Facing the dramatic increase of overweight and obesity in many countries, enhancing educational alimentation remains crucial to fight bad food habits. Alternatively, the identification of drugs that could boost

exercise endurance (Woldt et al. 2013) or either complement or even reproduce the anticancer effects of CR without drastic changes in diet and lifestyle (i.e., CR mimics) is a goal for many pharmaceutical companies (Hursting et al. 2009). Elucidating the mechanisms underlying the anticancer effects of CR and exploiting this mechanistic information to target calorie restriction-responsive pathways through combinations of dietary and pharmacologic approaches should permit in the future the development of effective cancer prevention strategies in humans.

The link between diet and cancer is not only quantitative, but dietary constituents have been shown to qualitatively modulate the complex multistage carcinogenesis process at the initiation, promotion, and progression phases of neoplasia (Milner et al. 2001; Go et al. 2003). This occurs because both essential nutrients and nonessential bioactive food components can alter many of the pathways of cancer, including apoptosis, cell cycle control, differentiation, inflammation, angiogenesis, DNA repair, and carcinogen metabolism (see Ross 2003, 2010 for review). This can also occur indirectly, through the modification of the microbiome that is increasingly recognized for its important functions in health and diseases, including cancer (Kinross and Darzi 2011; Cho and Blaser 2012; Schwabe and Jobin 2013). In humans, microbes, both commensal and pathogenic, are critical regulators of the host immune system and, ultimately, of inflammation. Consequently, microbes have the potential power to influence tumor progression as well, through a wide variety of routes, including chronic activation of inflammation, alteration of tumor microenvironment, induction of genotoxic responses and metabolism. The impact of gut microbiota in eliciting innate and adaptive immune responses beneficial for the host in the context of effective therapies against cancer has been highlighted recently: the anticancer efficacy of alkylating agents (such as cyclophosphamide) and platinum salts (oxaliplatin, cisplatin) is compromised in germ-free mice or animals treated with antibiotics (Viaud et al. 2013). Gut microbiota could also be involved in the link between obesity and increased cancer risk through overproduction of a DNA-damaging bile acid (Ohtani et al. 2014). It is relevant in this context to recall that the shift to modern diet habits is also characterized by significant qualitative changes (e.g., our ancestors evolved on a diet that included daily intake of fiber from a diversity of sources; Leach 2007). Improving our knowledge on the qualitative aspects of our ancestral bowels is important because they also conditioned our current nutritional parameters and physiological responses. The requirement range of particular nutrients may also be contingent upon the functionality of the cell and organism (Go et al. 2003). Certain nutrients may also be harmful in supernormal doses. Determining whether qualitative changes in our diets contribute to the presence of unused

resources and/or are equivalent to disturbances for our body is thus unclear at the moment. In general, despite considerable progress in our understanding of the relationship between diet and cancer much remains to be revealed with respect to the relationship between cancer risk and our exact dietary requirements, constituent absorption and metabolism (Schoenfeld and Ioannidis 2013).

The links between cancer and diet can be initiated early in life, commencing from embryogenesis and fetal development, through early childhood when complicated interactions of multiple environmental factors, including diet, influence the developmental trajectories and physiology resulting in subsequent increase in cancer risk later in life (Frankel et al. 1998). For example, *in utero* exposure to certain so-called epigenetic diets that affect key tumor-related gene expression through epigenetic regulation may lead to reprogramming of primary epigenetic profiles of the fetal genome, resulting in different susceptibility to diseases, including cancer (Li et al. 2014). For example, genistein in soybean products, sulforaphane in cruciferous vegetables, and epigallocatechin-3-gallate (EGCG) in green tea have been associated with a lower risk of developing several common cancers and are considered as dietary epigenetic modulators. Dietary epigenetic intervention could provide a cost-effective transgenerational human disease control, and the prenatal and/or postnatal dietary administration of epigenetic supplements (with chemopreventive potential) could lead to early cancer prevention (Li et al. 2014).

#### Avoiding disturbances to prevent cancer: an underestimated solution?

While loss of homeostasis is traditionally seen as a key initial step on the route to cancer development (Hanahan and Weinberg 2000, 2011), much remains to be performed to fully understand disturbances that weaken homeostasis at a level sufficient to initiate an invasive cancer. Defining disturbances in the context of cancer risk is challenging because it, firstly, concerns several levels of biological organizations, ranging from cells, tissues, organs, and individual. Secondly, the amplitude and timescale of disturbances, punctual or chronic episodes resulting from evolutionary mismatches between ancestral and modern life styles, can also be essential. At the moment, we mostly possess a qualitative knowledge, namely a list of variables/situations that favor cancer initiation by presumably acting as disturbances (depression, infections, lack of sleep, stress...), but we miss quantitative information on them (e.g., intensity, frequency, length of exposure) in the context of cancer risk. For instance, we know that immunosuppression, whatever its origin, can favor cancer progression, but we do not know precisely the shape of the relationship between the lengths of time people must stay in an immunosuppressive

state for an invasive cancer to progress until problematic stages. Undoubtedly, this relationship also depends on the complex interaction of individual parameters such as the age, psychology, life style, and genetic background. Furthermore, numerous cancers have an infectious causation (Zur Hausen 2009), and typically oncogenic pathogens induce disturbances at cellular level that favor cancerous transformation because they alter natural barriers to tumorigenesis (see Ewald 2009).

Only once precise quantitative data will be obtained on the links between disturbances and invasive cancer initiation, will it be possible to formulate realistic predictions on cancer probabilities in relationship with personal characteristics. It is increasingly acknowledged that accompanying actions such as psychological support and/or pain avoidance reduce oncogenic progression in cancerous patients (Chida et al. 2008). This is in accordance with the idea that disturbances have an exacerbating effect on cancerous progression. What we suggest here is that any actions that reduce the level of disturbances prior to the initiation of oncogenic progression should be developed because they are expected to prevent oncogenesis. This is indirectly supported by several studies linking different lifestyles and psychological profiles to cancer risk (Kreitler et al. 2013).

The elusive nature of malignancy initiations, and its progression until a threshold, above which it becomes problematic to stop, arises from the fact that it depends upon conditions that occur intermittently. One important corollary of this is that susceptibility to invasion by cancerous cells is not a static or permanent attribute, but a condition that fluctuates over time, with changes from year to year and even within a given year, as the amount of unused resources and of disturbances fluctuates. Establishing causative correlations between particular disturbing events during the life and subsequent cancer risk, sometimes years later, is undoubtedly challenging and should be studied first on animal models where genetic and ecological parameters can be experimentally controlled. This research should ultimately contribute to the development and efficiency of preventive behaviors by providing a clearer objective necessary for obtaining efficient protections against cancer. Finally, such knowledge should permit to develop concrete therapeutic preventive strategies. Being able to identify the episodic events during which cancer initiation and subsequent progression are likely to occur is indeed crucial, because it could lead to the development of novel preventive strategies that focus specifically on those critical periods.

Broadly, a first direction could rely on treatments whose basic principle is to prevent people from being in a disturbed state likely to promote carcinogenesis. This strategy has been tested in infectious diseases; for

instance, antibiotics are used in fragile patients with a viral infection to prevent subsequent bacterial infections that could develop in the immunosuppressed context induced or majored by the virus. A second possibility would be to propose treatments specifically against cancer initiation when people cannot avoid crossing a risky period. For example, a specific treatment against cancer cells can be proposed when people experience depressive disorders. Once again, this strategy is successfully applied in some infectious diseases, for example where antimalarial medication is recommended to people visiting a malaria-endemic region.

#### Environmental disturbance, infection and cancer

Oncogenic parasites, as a rule, cause cancer in only a small percentage of infected individuals. This finding and the high frequency of mutations in pathogen-induced cancers have led to the conclusion that pathogen-induced oncogenesis almost always requires mutations in hosts (Zur Hausen 2010). The corollary of this conclusion is that increased exposure to mutagens will increase the frequency of pathogen-induced cancers. Environmental disturbances that increase exposure to mutagens therefore can be expected to increase pathogen-induced cancers.

Although there is little evidence to test this prediction in wildlife, the available information is consistent with it. Chemical pollution and fibropapilloma-associated turtle herpesvirus have been associated with sea turtle fibropapillomatosis, and levels of polychlorinated biphenyls are elevated in the blubber of genital carcinoma of sea lions (Herbst and Klein 1995; Foley et al. 2005; Ylitalo et al. 2005; McAloose and Newton 2009). Depending on the species under consideration, environmental disturbances that increase exposure to mutagens may enrich or deplete resources. Correlations between environmental richness and cancers may therefore need to consider the possibility that infectious agents and mutagens contribute jointly to oncogenesis.

By altering population densities of oncogenic parasites, ecological disturbances can alter the rate at which they cause cancer. Dam building, for example, has increased the populations of alternate hosts of human parasites that play a role in cancer. Increases in snail populations increase rates of schistosome infection (Steinmann et al. 2006) and may thus increase rates of bladder cancer. Similarly, increases in mosquito density may increase malarial infections (Keiser et al. 2005) and thereby increase rates of Burkitt's lymphoma. As infectious agents of wildlife cancer are discovered, similar effects of human disturbances on cancer in wildlife through influences on the prevalence of infection will need to be investigated.



Viruses are particularly likely to be oncogenic agents in wildlife populations. As intracellular parasites, they often replicate their genomes by stimulating host cells to proliferate. This manipulation is accomplished by abrogating critical barriers to cancer, such as cell cycle arrest, apoptosis, and the maximum number divisions a cell can undergo (Ewald 2009; Ewald and Swain Ewald 2012). Viruses that have been associated with cancer in wildlife generally belong to viral groups that cause human cancers. In the summary of wildlife cancers associated viruses provided by McAloose and Newton (2009), for example, most of the implicated viruses accord with this generalization (Table 1). The human viruses in these groups are generally transmitted by sexual contact and saliva, and sometimes by milk and needle-borne blood (Table 1). Because these modes of transmission occur at infrequent intervals, they favor long-term persistence within individual hosts (Ewald and Swain Ewald 2013). A major mechanism by which such persistence is possible involves compromising the barriers to cancer mentioned above (Ewald and Swain Ewald 2012).

Although the transmission routes of viruses that are associated with cancer in wildlife are not well understood, these considerations regarding selection for persistence within hosts and the routes of transmission in humans suggest that oncogenic viruses in wildlife may be disproportionately transmitted by sexual contact, saliva, and milk. These modes of transmission often lead to geographic discontinuities of viruses or viral subtypes in human populations (e.g., human T-lymphotropic viruses) and presumably would do so in wildlife populations. If ecological disturbances allow geographically separated populations to come into contact, increases in infectious cancers would be expected in the newly unexposed

populations. Spread to populations of different species is also possible because oncogenic effects of viruses in related host species have been noted, for example, in the reticulo-endothelial cancer of galliformes, and the fibropapillomas of turtles (McAloose and Newton 2009).

Although the spread of oncogenic viruses among different populations of a given species in response to environmental disturbance has not been studied in wildlife, environmental disturbance has been implicated in the spread of human viruses that directly or indirectly contribute to human cancer. Oncogenic variants of the human papillomavirus have increased in association with conditions of warfare (Grce et al. 1996). Hepatitis C virus, which is a cause of human liver cancer, spread globally in response to new opportunities for blood-borne transmission (Markov et al. 2009). The human immunodeficiency virus, which contributes to cancer indirectly through immunosuppression, spread in humans during the early stages of the AIDS pandemic in response to changes that affected movements of human populations (Ewald 1994; Faria et al. 2014).

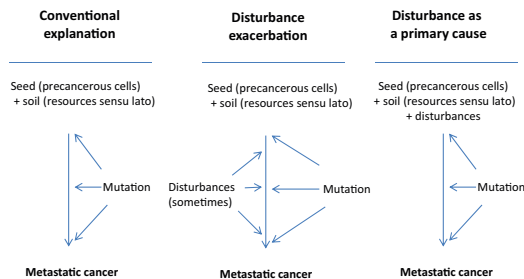
### Concluding remarks

The traditional seed-soil hypothesis (Paget 1896) stipulates that, for metastatic cancers to start, the soil is as important as the seed. However, in the context of primary tumor, evidence indicates that 'seeds' are virtually everywhere in the body with aging and, at least in western lifestyle where caloric intake is high (true also in poor countries in which exposure to toxics and oncogenic pathogens is high), the 'soil' basically provides constantly favorable conditions for seeds—cancer pro-

**Table 1.** Viruses associated with cancer in wildlife

Virus associated with cancer in nonhuman host	Hosts	Taxonomic group of viruses	Human cancer-associated viruses in same taxonomic group*	
			Virus	Transmission
Various retroviruses	Walleye pike ( <i>Sander vitreus</i> ); Atlantic salmon ( <i>Salmo salar</i> ); Attwater's prairie chicken ( <i>Tympanuchus cupido attwateri</i> )	Retroviridae	Human T-lymphotropic virus-1 (o)	Sex, milk, blood
Woodchuck hepatitis virus	Woodchuck ( <i>Marmota monax</i> )	Hepadnaviridae	Hepatitis B virus (o)	Sex, blood
Otarine herpesvirus-1	California sea lion ( <i>Zalophus californianus</i> )	Gamma herpesvirus	Epstein-Barr virus (o); Kaposi Sarcoma-associated herpesvirus (o)	Sex & saliva
Fibropapilloma-associated turtle herpesvirus	Sea turtle ( <i>Chelonia mydas</i> )	Alpha herpesvirus	Human herpes simplex virus-2(a)	Sex
Bandicoot papillomatosis	Western barred bandicoots	Papillomavirus–	1. Human papillomavirus (o)	1. Sexual contact
Carcinomatosis virus-1	( <i>Perameles bougainville</i> )	polyomavirus mosaic	2. Merkel cell polyomavirus (o)	2. probably saliva
Rana virus-1	Leopard frog ( <i>Rana pipiens</i> )	Iridoviridae	None	

\*(o) = oncogenic; (a) = cancer-associated and possibly oncogenic.



**Figure 3** (A) The standard seed-soil hypothesis as an explanation for oncogenesis, (B) When the first associations between disturbance and cancer began surfacing they were accommodated by fitting them into the seed-soil paradigm, and (C) Disturbances play a more direct role because they compromise protective barriers to oncogenesis.

genitor cells—to germinate. From an ecological perspective, we argue here that disturbances constitute another key interacting parameter to include into the reasoning. The role of disturbances in carcinogenesis is well documented and generally accepted, but probably underestimated as a primary cause (Fig. 3, case B versus case C). The distinction is crucial because preclusion of a primary cause prevents the disease, while inhibition of a secondary cause only reduces the frequency or severity of disease but does not prevent the disease itself. Ewald (2009) argued that we strongly underestimate the role of infections as cofactors of cancer initiation. We further argue here that we not only underestimate the role of disturbances and pathogens as cancer initiators, but also the role of additional factors, such as available resources and behavioral traits in potentially destabilizing homeostasis. As discussed above, it is challenging to act on both the seed presence and the soil suitability, but all the possibilities have not been sufficiently explored concerning the avoidance of disturbances. There is undoubtedly a very large range of disturbing effects, and causation is most of the time difficult to establish because time between cancer initiation and its detection is usually long. More ongoing research, especially in a quantitative context, should be performed to understand and potentially identify the range of disturbances that compromise natural barriers to cancer. Then, developing tools for monitoring homeostasis at all the different relevant scales should permit the identification of actual periods of the life that are the most at risks of the initiation of invasive cancers. From this knowledge, novel preventive strategies could be developed.

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**Résumé :**

Le cancer est une pathologie caractérisée par la transformation de cellules de l'organisme, et leur prolifération incontrôlée aux dépens de l'organisme. Elle peut toucher tout tissu de l'organisme, et menacer la survie des patients à terme. Ce phénomène est souvent interprété comme une dégénérescence de l'organisme au cours du vieillissement, mais ce paradigme ne suffit pas à embrasser toute la complexité de cette maladie. En effet, la progression cancéreuse est basée sur des mutations qui nourrissent une prolifération différentielle des cellules, et elle peut donc être décrite par une dynamique écologique et évolutive. En outre, les manifestations du cancer sont extrêmement répandues dans tout le vivant, et peuvent être attribuées à l'émergence des organismes multicellulaires il y a un milliard d'années. Le cancer a donc toujours représenté une contrainte sur l'évolution des organismes. La compréhension globale du cancer nécessite donc d'élucider comment les dynamiques éco-évolutives intra- et inter-organisme s'influencent mutuellement au cours des temps évolutifs. A l'aide de conceptualisation et d'approches théoriques, nous montrons qu'une approche multi-échelle offre de nouvelles perspectives sur les processus écologiques et évolutifs impliqués dans le cancer. A l'échelle intra-tumorale, nous nous concentrons sur les interactions entre cellules cancéreuses et au rôle structurant que ces interactions peuvent avoir dans les écosystèmes tumoraux. Nous montrons notamment que la fréquence des interactions diminue la diversité clonale durant l'expansion tumorale. A l'échelle populationnelle, nous formulons et explorons une hypothèse sur l'origine de la forte fréquence des cancers héréditaires : les défenses anti-cancer sélectionnées dans les environnements cancérogènes pourraient compenser la progression cancéreuse, et donc autoriser la persistance d'allèles pro-oncogéniques à l'équilibre mutation-dérive. Nous considérons enfin les interactions réciproques entre évolution des organismes et évolution des cellules cancéreuses : spécifiquement l'évolution emboîtée de la résistance et de la tolérance au cancer, et l'évolution de stratégies de manipulation de l'hôte chez les cellules cancéreuses. Nous montrons notamment que l'évolution intra-individuelle favorise la tolérance, tandis que l'évolution inter-individuelle favorise la résistance.

**Mots-clés :** cancer, écologie, évolution, approche multi-échelle

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**Abstract:**

Cancer is a pathology characterized by organism cell transformation and uncontrolled cell proliferation at the expense of the organism. It can affect any tissue in the organism, and can eventually threaten patient survival. This phenomenon is commonly viewed as the result of organism decay during ageing, yet this paradigm fails to embrace the whole complexity of this disease. Cancer progression indeed relies on mutations which fuel differential cell proliferation, and thus it can be described by ecological and evolutionary dynamics. Besides, cancer manifestations are widespread across living organisms, and may be due to the emergence of multicellularity a billion years ago. Cancer has thus always constrained the evolution of organisms. How intra- and inter-organism eco-evolutionary dynamics influence each other across evolutionary times must be investigated to fully understand cancer. Through conceptualization and theoretical approaches, we show that a multi-scale approach offers novel prospects on ecological and evolutionary processes involved in cancer. At intratumor scale, we focus on interactions between cancer cells and on how these interactions structure tumor ecosystems. We notably find that frequent interactions yields lower clonal diversity during tumor expansion. At the population scale, we aim to explain the origins of highly frequent hereditary cancers. We thus hypothesize that pro-oncogenic alleles may neutrally evolve in certain contexts: anti-cancer defenses that are selected in carcinogenic environments may actually compensate cancer progression, and thus allow pro-oncogenic alleles to persist at mutation-drift equilibrium. We finally explore the reciprocal interactions between organism evolution and cancer evolution: especially, we use a nested approach to predict the evolution of resistance and tolerance to cancer, and then we suggest that cancer cells may evolve host manipulation strategies. We notably find that intra-individual evolution favors tolerance over resistance, whereas inter-individual evolution rather favors resistance.

**Keywords:** cancer, ecology, evolution, multi-scale approach