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Evolutionary biology of cancer

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Cancer is driven by the somatic evolution of cell lineages that have escaped controls on replication and by the population-level evolution of genes that influence cancer risk. We describe here how recent evolutionary ecological studies have elucidated the roles of predation by the immune system and competition among normal and cancerous cells in the somatic evolution of cancer. Recent analyses of the evolution of cancer at the population level show how rapid changes in human environments have augmented cancer risk, how strong selection has frequently led to increased cancer risk as a byproduct, and how anticancer selection has led to tumor-suppression systems, tissue designs that slow somatic evolution, constraints on morphological evolution and even senescence itself. We discuss how applications of the tools of ecology and evolutionary biology are poised to revolutionize our understanding and treatment of this disease.

For ecologists and evolutionary biologists, natural selection and evolution are usually viewed as the domain of peppered moths and finches, driven to adapt by predators and competition. Indeed, few students of Darwin and Macarthur would conceive that their field of biology could have a pivotal role in our understanding and fighting of complex diseases such as cancer. Molecular biologists have, by curious contrast, long recognized carcinogenesis as an evolutionary process involving natural selection among 'renegade' cells [1]. However, the evolutionary forces that result in cancer have recently come under the focused scrutiny of evolutionary biologists and ecologists, and this disciplinary crossover has begun to yield significant insights.

Familiar natural selection involves variation in lifetime reproductive success among genetically variable individuals, with adaptive genetic and phenotypic changes accumulating across generations via relatively successful germ lines. Cells within the metazoan body are, for the most part, genetically identical; thus, they have evolved an altruistic division of labor represented by diverse, specialized and integrated types of tissue. By contrast, the somatic selection of cancer is driven by differential replication of cells that differ phenotypically as a result of genetic mutation and epigenetic alteration (Table 1).

Cancer risk appears to follow more or less inevitably from the combination of multicellularity, cell replacement, and genetic and epigenetic changes that occurs over long time periods [1,2]. The origin of each genetically distinct cancer cell lineage has been likened to the sympatric origin of a new asexual species, competing with its progenitors and neighbors for cellular resources. The development of most cancers requires a series of nested mutations in caretaker, gatekeeper, landscaper and other genes (see Glossary) [3] whereby six 'hallmarks of cancer' are acquired: (i) self-sufficiency of cells in signals controlling growth; (ii) loss of sensitivity to antigrowth signals; (iii) evasion of apoptosis via mutation or loss of gatekeeper genes; (iv) development of limitless replicative potential, usually via the expression of telomerase; (v) sustained angiogenesis, whereby the blood supply to a tumor is augmented; and (vi) tissue invasion and metastasis, which causes 90% of cancer deaths [4]. The acquisition of these

Table 1. Contrasts between the evolution of individuals in populations and cancer cells in individuals

Process	Evolution of populations	Evolution of cancer cells
Phenotypic variation generated	Germline mutation and recombination	Somatic mutation Epigenetic alteration Genomic instability
Selection	Owing to differential survival and reproduction; main selective agents are abiotic factors, competitors, predators and parasites	Owing to differential replication and apoptosis or cellular senescence; selective pressures include intercellular competition for resources, immunosurveillance and signaling system components such as receptors and hormones
Drift	Stochastic changes in allele frequencies, owing to sampling error in small populations of individuals	Stochastic changes in genetic or epigenetic allele frequencies, owing to sampling error in small populations of cells
Inheritance	Genes transmitted intact barring mutation or recombination	Asexuality; genetic and epigenetic variants inherited intact barring mutation or epigenetic alteration
Result of process	Adaptation across generations	Large cell population adapted to rapid growth, resulting in death of the individual

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Glossary

Apoptosis: programmed cell death.
Caretaker genes: genes that help maintain genetic integrity; their mutation can lead to microsatellite or chromosomal instability.
Cellular senescence: programmed cellular quiescence; cell persists but cannot replicate.
Chromosomal instability: increased rate of gain or loss of whole chromosomes or parts of chromosomes during mitosis, which can lead to loss of tumor suppressor genes and gains of oncogenes.
Epigenetics: regulation of gene expression by DNA methylation patterns, which are inherited as presence or absence of methyl groups at CpG sites (the epigenetic code), but can mutate or be reprogrammed during carcinogenesis.
Gatekeeper genes: genes that regulate growth and differentiation, which include oncogenes and tumor suppressor genes.
Genomic instability: increased rate of alterations in DNA owing to microsatellite or chromosomal instability.
Genomic imprinting: 'marking' of genes, via methylation of CpG sites, as to their parent of origin, paternal or maternal.
Green-beard mutations: mutations in self-binding cell adhesion molecules, such as cadherins, that lead to preferential fitness-enhancing interactions between specific alleles.
Immunosurveillance: immune system control of incipient tumors.
Landscaper genes: genes that, when mutated, lead to an abnormal extracellular and intercellular environment that contributes to carcinogenesis.
Microsatellite instability: genomic instability owing to deficiency in mismatch repair, which leads to a high rate of point mutations and mutations at microsatellite loci.
Oncogene: a gene that directly promotes cancer when abnormally activated.
***p53*:** a 'master' tumor suppressor gene, that is mutated in most cancers, and also mediates the tradeoff between cancer and longevity.
Positive selection: directional selection for specific changes in DNA sequence, usually involving amino acid substitutions that enhance protein function in some context.
Stem cell: a precursor cell that can renew itself and give rise to cells that undergo differentiation.
Tumor suppressor gene: gene that when lost or inactivated increases the chance of developing cancer.

hallmarks is an evolutionary and a developmental process involving selection among variant cells, the stabilization of gene expression patterns and heterochronic changes toward less differentiated states [5]. Whether a new cellular 'asexual species' survives and proliferates depends upon its interactions with other cells and how the processes of somatic evolution promote its trajectory of genetic and phenotypic change.

The ecological theatre of carcinogenesis

Ecological interactions between individuals and species, particularly predation and competition, drive evolution by natural selection. Recent conceptions of cancer biology, based on population biology and evolutionary theory, have demonstrated how these same selective agents drive the somatic evolution of cancer [6–10].

Predation

In ecological interactions among individuals, predators can control the population sizes of prey and select for antipredator adaptations, whereas the risk of predation can trade off with foraging ability. The cellular analogue of predation is immune system attack on cells recognized as foreign or otherwise aberrant, which has recently been demonstrated as crucial to the early stages of natural cancer suppression [11,12]. Thus, the immune system engages in continual 'immunosurveillance' for cells exhibiting unusual antigen profiles, which 'natural killer cells' help to destroy. But predation by the immune system also apparently selects for cancer cell escape variants that are less immunogenic [12], just as chemotherapy selects for chemo-resistant cells [13]. Iwasa *et al.* [14] analyzed the dynamics of intervention and escape systems, showing how outcomes depend crucially on cancer cell population sizes, mutation rates, the number of mutations required for escape and the efficacy of the intervention.

Do cancer cells have other antipredator adaptations? Alpha-defensins are antimicrobial genes that are highly overexpressed in some cancers (e.g. lung and renal cancer) apparently to create a microenvironment that is unfavorable for the adaptive immune system [15]. Moreover, many tumors (e.g. breast and renal) often develop in low-oxygen tissue environments before becoming vascularized [16], and such environments are unfavorable for effective immune function; might foraging–predation risk tradeoffs shape the somatic evolution of cancers? Future studies taking an evolutionary-ecological perspective could uncover novel adaptations of cancer cells, and elucidate the tradeoffs under which they evolve.

Competition

In the world of finches and warblers, competition within and between species is a major force in generating adaptations, structuring communities of interacting species and selecting for dispersal. The cellular sphere is usually dominated by cells that are constrained by diverse mechanisms not to compete with each other, but this sphere also harbors arenas of competition among cancerous and normal cells. Recent studies have demonstrated the crucial roles of the integrity of the local cellular environment, intercellular interaction, and trophic adaptations of groups of cells in somatic evolution at this microscopic level [17–19].

Similar to individuals, cells exist in a complex interactive environment. The cellular niche or habitat is structured by contacts with the extracellular matrix as well as with other cells, and such contacts can control cell growth. Thus, stem cell proliferation can be controlled by the cellular microenvironment, and damage to this environment can initiate carcinogenesis [17]. Michor *et al.* [18] discuss how alterations in landscaper genes can create an abnormal cellular niche that contributes to cancer and, indeed, such abnormalities can also be generated by the processes of apoptosis and cellular senescence that suppress cancer [19].

A new clone of cancer cells competes with neighboring cells for food and services, such as waste removal, initially within its natal environment. When tumors have grown to a certain small size, their growth becomes limited by their ability to obtain cellular resources, and they normally develop a 'glycolytic phenotype' that involves energy production by glycolysis in a hypoxic environment [16,20]. Using a novel cellular ecological perspective, Gatenby and Gillies [16] interpreted this phenotype as an adaptation: the metabolic activity of tumor cells leads to local acidosis that is toxic to neighboring normal cells, as well as facilitating the degradation of the extracellular matrix. These changes provide tumor cells with a strong competitive advantage that fosters growth and invasion, similar to the adaptations of allelopathy in plants or bacteriocins in microbes. Moreover, this adaptation of

tumors often involves a specific amino acid change in the *p53* tumor suppressor gene during somatic evolution, a molecular adaptation that has evolved convergently in the *p53* gene of hypoxia-stressed *Spalax* mole rats during evolution at the level of populations [21].

The intrinsic limitations of tumor growth, in the absence of supporting blood vessels to provide food and remove wastes, lead to strong selection for vascularization, and angiogenesis (i.e. formation of new blood vessels) can also be viewed as a competitive adaptation [5,7,8]. As tumors enlarge, and develop or recruit vascular tissue, they can become more heterogeneous both genetically and phenotypically [22], comprising a mix of cancerous and healthy cell types that cooperate as an integrated tissue but also compete for food and space. Nagy [23] developed an evolutionary ecological model that incorporated tumor heterogeneity and showed that interactions in such cellular communities could lead to competitive exclusion of cell lineages, in some situations giving rise to 'hypertumors' that exploit the developed vasculature to grow more quickly than do other cancer cell clones, but then die because they do not have a capacity to support further angiogenesis. He described how indirect evidence from the histology of some cancers supports the existence of hypertumors, and how the evolved balance between cooperation and competition in tumors has crucial clinical implications for optimizing cancer therapies.

The maintenance of diversity in tumors might also be influenced by competition between genetically different cancer cell populations, just as competition can maintain diversity in ecological communities at the population and species levels. Recent mapping of tumors has shown them to be arranged in mosaic patterns of cell populations that differ in genotype, and a computational model based on the empirical data demonstrates that the coexistence of similar cancer-lineage competitors might be enhanced by such spatial dynamics, without a need to invoke variable mutations rates, neutrality, or effects of clonal age [24]. Gonzalez-Garcia *et al.* [24] thus suggest that the theory of spatial ecology helps to explain the maintenance of genetic diversity within tumors, as well as the diversity of macroscopic life.

Cellular ecology might be as complex as that of multispecies communities, with the joint, concurrent effects of predation and competition selecting for a range of traits. The evolution of cancer cells is characterized by a series of selective sweeps of favored genes, followed by clonal expansions [3,9,25,26]. However, as Ronald Fisher noted [27], natural selection is not evolution. Understanding the entire evolutionary play requires consideration of how genetic and phenotypic variation are generated at the somatic cellular level and how non-selective processes, such as genetic drift, might also have key roles in the fates of genes, cells, tissues and individuals.

The evolutionary play of somatic evolution

The paradox of variation

Genetic variation provides the essential raw material for somatic and population-level evolution (Table 1), and more variation might often result in faster evolution. Many cancers develop forms of 'genomic instability' that greatly increase levels of genetic variation among cells and accelerate the rate of somatic evolution in carcinogenesis. Genomic instability is crucially important to the development of malignancy for many types of cancer [3,28].

Traditionally, genomic instability has been viewed as a process that enables the faster evolution of cancer cells. By contrast, Breivik and Gaudernack [29] and Komarova and Wodarz [30] point out that, because most mutations, particularly large ones, are deleterious, genomic instability is unlikely to be favored by selection for higher mutation rates. Brevik and Gaudernack [10,29] proposed a solution to this paradox of variation: that mutagenic environments not only produce mutations directly, but also select for cells that avoid the time and energy costs of repairing mutations and thereby gain a strong growth advantage. Thus, although a harsh cellular environment selects for more-extensive repair, it also selects for increased benefits from not repairing DNA damage. Breivik and Gaudernack [29] support this reasoning with a model of the costs and benefits of repair, and with evidence that specific types of mutagen (methylating mutagens versus 'bulky-adduct forming' mutagens, such as UV and free radicals) generate the expected form of genomic instability (microsatellite versus chromosomal) in cancers along the proximal-distal region of the colon. Indeed, some cancer lineages have apparently optimized their rate of chromosomal mutation [31], thereby increasing cellular replication via the loss of tumor suppressor genes but keeping deleterious mutations from dropping cells below the 'error threshold' of irreversible maladaptation [32].

Selection for increased mutation rate in cancers has crucial implications for cancer therapy because many chemotherapeutic agents are themselves selective mutagens that might promote the instability that ultimately renders them ineffective [31]. Indeed, the degree of aneuploidy and polyploidy in cancers is highly correlated with disease severity [3]; it might be that polyploidy of cancers is adaptive in the same selective context as polyploidy of plants and animals, where it facilitates invasion of harsh environments [33].

Drift and population size writ small

At the population level, the genetic drift of neutral alleles in small populations leads to the random loss of allelic diversity, and neutral alleles linked to selected ones can 'hitchhike' to fixation. The same processes occur at the cellular level. Thus, the rate of loss of tumor suppressor genes depends on the local population size of cells [34], and the random loss of stem cells leads to mutation accumulation without phenotypic change [17]. Clonal expansion via selective sweeps of cancer cell lineages with a favored mutation can also fix neutral alleles that are necessary for the cancer phenotype, even in the absence of effects on cell proliferation or mutation rate [6,9,25,26] (Figure 1). Maley and Forrest [6] developed the first agent-based model to examine the interaction of neutral, selected and mutator alleles in the evolution of cancer, which demonstrated that the interplay of drift and selection depended crucially, and non-intuitively, on whether the mutator phenotype was expressed. The predictions of such models, and others

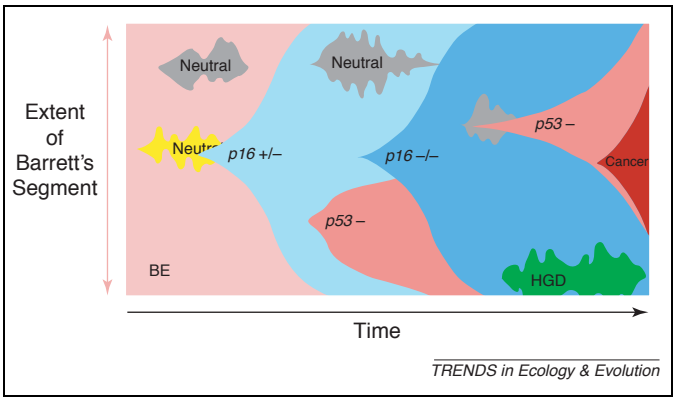

Figure 1. Evolution in a hypothetical case of Barrett's esophagus, a cancer of the esophagus [25,26]. The colors represent different clones of cells (with pink as normal), and the vertical axis represents the spatial spread of the afflicted cells. As in the evolution of asexual populations, the evolution of cell lineages proceeds via a series of temporally nested mutations. *p16* and *p53* are tumor suppressor genes that, when mutated from wild type (/) to losses of function (/ and /), can lead to selective sweeps as a result of their effects on cell proliferation; neutral mutations (which might be necessary for the eventual expression of cancer) can be carried to fixation by hitchhiking (as for the yellow zone), or lost (as in the gray zones) Other neutral or selected mutations, and 'high-grade dysplasias' (HGD) (i.e. severe, precancerous tissue changes) can arise and be lost by drift, interclonal competition, or other mechanisms. 'Cancer' in red refers to cells with all of the hallmarks of cancer. Barrett's esophagus, and other cancers, develop via the asexual evolution of genetic and epigenetic changes by selection and drift, which occurs in more or less predictable sequences.

based on evolutionary dynamics of drift and selection, are now being tested empirically using clinical systems such as Barrett's esophagus, which enables the spatial and temporal analysis of the genetic stages of cancer progression (Figure 1) [9]. These theoretical and empirical analyses demonstrate that drift has a crucial role in the adaptive cellular evolution of cancer.

Oncogenetic trees

Evolution at any level typically yields phylogenies, which can be used to infer past events, analyze the causes of diversification and test for convergence. During somatic evolution, phylogenies reconstructed using the genetic diversity of cancer cells can be used to infer the timing and sequence of changes in gatekeeper, caretaker and landscaper genes. Shibata [35] and Tsao *et al.* [36] pioneered the use of molecular clocks based on microsatellite mutations to infer genetic pathways to cancer, demonstrating a long period of 'invisible' progression before phenotypic cellular changes. Similarly, Jiang *et al.* [37] and Tarafa *et al.* [38] used karyotype change, generated by chromosomal instability, to test for convergent and divergent pathways. They showed that instability arises early in cancer progression, and that some types of tumor exhibit several distinct routes from normal to cancer cells, with genetic alterations tending to occur in particular orders. Given the accelerating power of statistical phylogenetic inference, genome-sequencing methods, and methods for inferring demographic histories of population expansion [39], further use of oncogenetic trees should yield novel insights into the patterns and processes of somatic evolution.

Evolution of cancer risk and anticancer adaptation

Episodes of somatic evolution within organisms alternate with more-familiar evolution at the level of populations, as genes related to cancer evolve across generations. The evolution of such genes is driven not only by the negative effects of cancer, but also by a diversity of selective forces centered around the evolving physiological functions of the genes in cell survival, interaction and growth.

Evolution of genes and genetic systems promoting cancer

Recent studies have shown how genes promoting cancer can spread via the pleiotropic effects of strong selection in other contexts [40,41]. Thus, pediatric cancers are rare, apparently as a result of their strongly negative fitness effects, but they are concentrated in two tissues, brain and bone, that have undergone striking recent evolutionary increases in size and growth trajectories along the human lineage. Such effects might have arisen as a byproduct of rapid shifts in the rate and timing of cell proliferation systems [42,43]. Similarly, a third tissue with high pediatric cancer rates, white blood cells, is subject to the effects of strong selection from host–parasite coevolution [41].

Rapid evolution is expected to generate evolutionary disequilibrium that is corrected over time, but antagonistic coevolution might drive ongoing continual change that engenders some degree of maladaptation in one or both of the conflicting parties. Recently, a suite of genes involved in carcinogenesis have been shown to exhibit signatures of positive selection [44–46] and, in each case, this selection appears to involve evolutionary antagonisms, such as those seen in parent–offspring conflict, sexual conflict, sexually selected conflict or intragenomic conflict [46–48].

Kleene [47] describes how intragenomic conflict and sexual selection might both characterize genes involved in spermatogenesis, and that many of these genes promote rapid cell replication and exhibit unusual patterns of expression (such as dramatic overexpression) in cells involved in spermatogenesis and in malignant cells. Indeed, a whole suite of 'cancer-testis-associated (CTA) genes' is expressed only in the testes and malignant cells [47], and some of these genes have been subject to strong positive selection among species. Thus, genetic pathways involving CTA genes, which evolved in the context of sexual conflict and sexual selection, are apparently co-opted by cancer cell lineages during somatic evolution, as developing cancer cells avoid apoptosis, dedifferentiate and take on properties of immortal male germ cells (5,46,47).

Parent–offspring conflict might also promote the evolution of increased cancer risk, as a result of 'tugs-of-war' over resources during gestation [49] mediated by invasiveness of placentation [50,51] and other physiological processes of pregnancy. For example, cadherins, a class of homophilic self-recognition proteins involved in cell adhesion and tissue invasion in both placentation and carcinogenesis, might be prone to positively selected 'green-beard' mutations during placental development, which favor the specific allele involved but harm other alleles [52,53]. Similarly, Zhang and Rosenberg [44] suggested that the positive selection that they inferred on the *ANG* gene, which is instrumental in angiogenesis during placentation as well as cancer, was related to maternal–fetal conflict. Parent–offspring conflict might also

Box 1. Cancer in ancestral versus current environments: the double-edged sword of progress

Humans provide an outstanding example of a species that is subject to rapid, self-imposed environmental changes, which recent studies have linked to cancer [56,59,67,68]. We focus here on two of the primary recent ecological changes relevant to human cancer risk: diet and reproductive life history.

With the advent of the agricultural revolution, most humans underwent a radical shift in diet, from >3000 types of plants and fruit to ~20 main types (mainly grains and sugars), and from lean game to domestic animal meat and dairy products [56,69]. With this dietary shift came increases in chronic diseases such as cancer, which appear less frequently in hunter-gatherer and many traditional societies [56,57,69]. High caloric intake itself also increases the risk of many cancers [58,70], and even moderate caloric restriction leads to striking reductions in cancer rates, as well as increasing lifespan independent of cancer risk [70,71]. Evolutionary theory has provided two main hypotheses for these effects: (i) antagonistic pleiotropy between early fitness effects, such as large body size, and cancer risk late in life [57,58]; and (ii) adaptive life-historical shifts to somatic maintenance during periods of low food supply [72].

Humans have also undergone recent radical shifts in the timing of female reproductive life history. In hunter-gatherers, and also presumably in ancestral human societies, the reproductive life history of women was characterized by a considerably later age of menarche (first menstruation), first reproduction much sooner after menarche, and longer periods of lactational amenorrhea [67,68]. These recent changes in life-history timing conspire to increase the rates of breast, endometrial and ovary cancer in modern societies, owing to: (i) the longer period from menarche to lactation, during which breast tissue is not yet fully differentiated; (ii) lower rates of breast feeding; and (iii) increased lifetime numbers of hormonal cycles [67,68].

Another recent adaptive evolutionary change in female life history has also led to increased cancer rates, although indirectly. Caspari and Lee [73] provide paleontological data for a rapid increase in human lifespan in the early upper Paleolithic, which they attribute to the evolution of kin-selected benefits from grandmothering. This hypothesis has received strong support from recent research showing that the local presence of grandmothers leads to increased fitness of descendant kin [74]. Such selection for lifespan extension is expected to increase the selective impact of cancer, because the development of most cancers is tightly linked to age [39].

enhance the risk of cancer via effects of genomically imprinted genes [49] that mediate transfer of resources from mother to fetus. Losses and gains of genomic imprinting are strongly associated with cancer [54], owing to the functional haploidy of imprinted genes and their roles in control over cellular resources during development [49]. These studies suggest that conflicts over control of cellular resources often lead to the evolution of genetic and epigenetic systems [54,55] that increase cancer risk.

Finally, although genetic and epigenetic factors have key roles in promoting carcinogenesis, most cancers exhibit a strong environmental component owing to the effects of carcinogens and other physiological factors, such as hormones and growth factors [56–58]. Rapid changes in ecological traits such as diet and life history might therefore drive increased cancer risk, as a result of maladaptive mismatches between ancestral and current environments [59] (Box 1).

Evolution of anticancer adaptations

Tumor suppressor systems are a primary line of defense against the development of cancer. Some tumor suppressor genes encode proteins that are involved in the detection of potentially oncogenetic damage to DNA or other cellular insults, followed by either repair, cellular senescence, or apoptosis [1,28], and these genes evolve both somatically within the body and across generations.

Nunney [60,61] and Frank [62] have recently provided the first comprehensive applications of population-genetic theory to understanding the genetic basis of cancer, with a focus on tumor suppression. Nunney [60,61] described why polygenic inheritance is expected for most genetic effects on cancer predisposition, and how the proportion of cancer in a population owing to heritable variation should be highest when the number of tumor suppressor loci just exceeds the line of indifference for a new allele to be favored. Frank [63] used a computational model of a genetic control network to demonstrate that additional layers of control provide diminishing protection against cancer, owing to the increased number of hereditary cancer-predisposition alleles that are maintained in the system as the number of layers increases.

The somatic evolutionary dynamics of tumor suppressor gene inactivation have recently been modelled by Komarova *et al.* [64] and Nowak *et al.* [34], who showed how this stage in cancer progression depends on cell population size, mutation rate, selection and the timing of genomic instability. Nunney [60,61] generated population-level models to predict the number of such loci expressed in different tissues and species; these studies show how the number of genes recruited to control cell proliferation should depend on the number of cells in a tissue, the number of cell divisions, mutation rate, lifespan and the degree of cancer-induced loss of fitness. Diminishing benefits of additional tumor suppressors might have selected for enhanced sophistication of those already present. Indeed, *p53*, arguably the most important tumor suppressor in the animal genome, is considered a 'master gene of diversity' [65] owing to its complex pleiotropic effects, which include mediation of the tradeoff between cancer risk and apoptosis-induced ageing [19].

Tumor suppression genes function at the cellular level. Recent studies demonstrate how adaptations for suppression of cancer have also evolved at the tissue level, whereby groups of cells are organized into compartments whose local cell-population sizes, proportions of stem cells versus differentiating cells and patterns of cell division influence cancer predisposition (Box 2). These studies provide outstanding examples of how optimization theory, population-genetic theory and the analysis of tradeoffs can be applied at the levels of cells and tissues, with implications for evolutionary theory and anticancer therapies.

Macroevolutionary effects of cancer risk and anticancer adaptations

Several recent studies have provided evidence that, in reducing cancer risks, natural selection generates macroevolutionary constraints on morphology and development [40–43]. For example, a variant number of cervical vertebrae are strongly linked to pediatric cancer in humans, and the number of cervical vertebrae is highly conserved among most mammals [66]. These data, and

Box 2. Optimal tissue architecture for cancer suppression

Recent theoretical studies have suggested crucial roles for three different aspects of tissue architecture in controlling the initiation and progression of cancer via mutated gatekeeper and caretaker genes [75–81].

First, the separation of tissues into long-lived rarely dividing stem cells and short-lived transit cells might represent an important anticancer adaptation [75]. Such separation might enable transit cells to be removed (i.e. shed) before they accumulate enough mutations to become cancerous. The division of cells into compartments consisting of stem cells and differentiated cells, with gradual replacement of differentiated cells, creates a 'linear process' that might have evolved as a mechanism to reduce the risk of cancer [75].

Second, theoretical analyses indicate an optimal stem cell:transit cell ratio within compartments [76]: too high a ratio increases the risk of dangerous mutations accumulating in stem cells, whereas too low a ratio decreases the ability of the stem cells to replace mutant transit cell lineages within compartments. Cancerous mutations are also more likely in longer stem-cell lineages [77], a problem that could be ameliorated via two hypothesized means of tissue renewal [78]: (i) a pool of quiescent proto-stem cells might contain a single dividing cell to replace each lost transit cell lineage, with the dividing stem cell replaced by a new cell from the pool [78]; and (ii) a compartment could be divided into a hierarchical series of stages, with an ultimate stem cell lineage that rarely divides and a series of lineages descending from it that divide with progressively greater frequency [78].

Third, the separation of tissues into different compartments also limits the initial spread of cancer clones, and the number of cells in compartments has conflicting influences on the within-compartment fixation of gatekeeper and caretaker genes [79–81]. In large compartments, caretaker mutations are at a competitive disadvantage owing to the negative effects of genomic instability, but gatekeeper mutations that enhance cellular replication can increase in a deterministic fashion (Figure Ia). By contrast, in small compartments, caretaker mutations might more easily be fixed by drift, and gatekeeper mutations are more readily lost (Figure Ib). Depending upon the parameters of the models, there might be an optimal compartment size that minimizes the local risk of cancer [81].

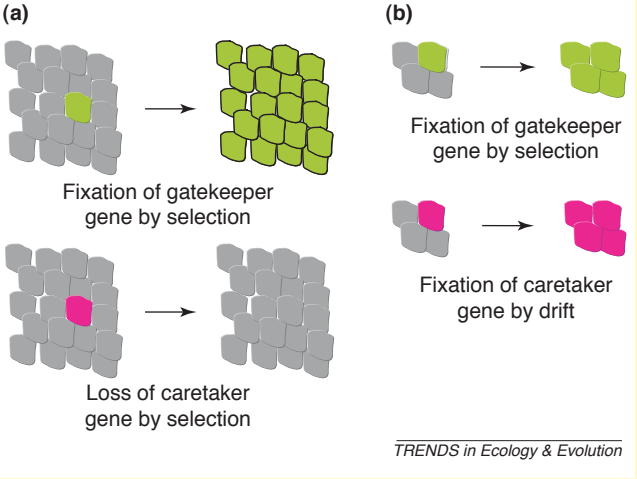

Figure I.

Box 3. Clinical implications: the enemy that evolves

Cancer is often intractable and fatal because it evolves, inexorably generating variants that differ in cellular adaptedness, and reacting to immunosurveillance or chemotherapy via evolved resistance in the surviving cells. Consideration of the evolutionary basis of the somatic development of cancer, and how its genetic underpinnings are selected over macroevolutionary time, should lead to novel research and clinical strategies.

Somatic evolution

Evolution-based treatment of cancer must apply therapies that counter, bypass or exploit its somatic evolutionary potential. One way is to attack essential aspects of the cancer phenotype, such as by suppressing angiogenesis. Alternatively, given the primacy of genomic instability in the evolutionary potential of cancer, chemotherapeutic agents can be targeted towards preventing or delaying its onset, or they can be used to alter the competitive dynamics of normal and cancer cells [31]. After cancer has a foothold, the competitive dynamics among normal and cancerous cells could be altered by strengthening the normal, benign cells at the borderline of the cancer, or by using a nutrient or mitogen that selects for chemosensitive cancer cells, then applying the true therapeutic agent to cancer cells 'set up' for death [82]. Finally, development of an evolutionary framework for relating genetic change, histological (tissue-level) change and the likelihood of clonal expansion or metastasis will provide the first integrative, predictive system for understanding carcinogenesis [83].

Macroevolution

The hunt for genes related to cancer could be accelerated by evaluating for cancer-risk genes that have been subject to rapid evolution along the human lineage, with special emphasis on those that are expressed during gamete, embryonic and placental development [46,47,51]. Such genes, and known oncogenes and tumor suppressors, should also be sequenced in a much wider range of primates and other mammals, to identify positively selected amino acid sites and link adaptive molecular evolution to aspects of life history and mating systems. Such application of a comparative, phylogenetic perspective to analyze the evolution of cancer is in its infancy, but holds tremendous promise. Comparative viewpoints on cancer also lead directly to concerns that animal models, such as mice, have less applicability to humans than is currently believed, because anticancer adaptations should be more or less unique to each species [60] and artificial selection inadvertently applied to laboratory animals has fundamentally altered their physiology and life history [41,84].

similar links to cancer for variation in number of ribs in humans and mice [66], suggest that anticancer selection strongly selects against morphogenetic variants and leads to evolutionary conservatism in morphology [40,66]. Such selection is mediated by balances between cell proliferation and differentiation [43]; indeed, many genes involved in embryogenesis are also proto-oncogenes (genes that can mutate to oncogenes) or tumor suppressor genes (some of which control the extensive apoptosis that characterizes normal development), and cancer commonly involves cellular dedifferentiation to a more or less embryonic state [5]. Taken together, these analyses, and the studies of pediatric cancers described above, suggest that anticancer selection sharply biases and limits the evolution of development and morphology, but that when strong selection in some context overcomes these constraints, increased cancer rates evolve as a more or less transitory evolutionary byproduct [2].

Conclusions

Cancer cells and cancer-related genes evolve under the same rules as peppered moths and finches. However, the training and specializations of cancer biologists, evolutionary biologists and ecologists have thus far largely precluded innovative interactions among these disciplines. As the theory and analytic tools of evolution and ecology might usefully be applied to study and treat

cancer from computer to laboratory to clinic (Box 3), analyses of how cancer evolves should also provide novel insights into outstanding questions in evolutionary ecology [43,47,48,55,63,66]. Only through integrated molecular, ecological and evolutionary analyses of cancer, at the somatic, population and macroevolutionary levels, will we come to understand and govern this unique disease.

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