Nature Reviews Cancer | AOP, published online 11 November 2013; doi:10.1038/nrc3606

PERSPECTIVES

OPINION

Life history trade-offs in cancer evolution

C. Athena Aktipis, Amy M. Boddy, Robert A. Gatenby, Joel S. Brown and Carlo C. Maley

Abstract | Somatic evolution during cancer progression and therapy results in tumour cells that show a wide range of phenotypes, which include rapid proliferation and quiescence. Evolutionary life history theory may help us to understand the diversity of these phenotypes. Fast life history organisms reproduce rapidly, whereas those with slow life histories show less fecundity and invest more resources in survival. Life history theory also provides an evolutionary framework for phenotypic plasticity, which has potential implications for understanding 'cancer stem cells'. Life history theory suggests that different therapy dosing schedules might select for fast or slow life history cell phenotypes, with important clinical consequences.

Cancers have been historically viewed as diseases of rapid cell proliferation and uncontrolled cell growth. However, cancers must also evolve survival or 'hardiness' strategies to persist in challenging environments, which may include hypoxia, acidosis and a predatory immune response. It is likely that these adaptations considerably contribute to the ability of tumours to metastasize to other organs and to survive toxic therapies. Life history theory — a theoretical framework from organismal evolutionary biology[1] — suggests that cancer cells may be subject to trade-offs between maximizing cell survival (by having an increased tolerance to unfavourable conditions) and maximizing cell growth; they are the cellular equivalents of the fabled 'tortoises' and 'hares'. In cancer evolution both strategies can be successful depending on the environmental conditions, and both strategies have important clinical implications for cancer patients.

In general, evolutionary life history theory proposes that several trade-offs help to determine the evolution of phenotypes. These trade-offs apply to all living things that are subject to natural selection and therefore should also apply to neoplastic cells. The three most important trade-offs that have been identified are those between reproduction and survival; producing offspring as soon as possible and producing offspring later; and offspring number and offspring quality[2]. Life history theory was developed from the observation that — despite the fact that each living organism has a unique natural history — the life histories of all organisms seem to lie along the 'axes' that are defined by the three major life history trade-offs. In long-lived mammals, such as elephants (*Loxodonta africana*), the adaptive strategy places an emphasis on survival over offspring; delayed maturation and longevity; and fewer but higher quality offspring. By contrast, small mammals such as meadow voles (*Microtus pennsylvanicus*) have low survival, rapid maturation and frequent, large litters of young. In many species, frequent and prolific reproduction comes at the cost of a decrease in longevity[3]; for example, the lifespans of the burying beetle (*Nicrophorus orbicollis*) and the fruitfly (*Drosophila melanogaster*) are significantly shortened by reproduction[4–6]. In a dividing cell there is no separation between the number and the timing of offspring. Cells can only divide rapidly or slowly. Therefore, the trade-offs between producing offspring as soon as possible and producing offspring later, and between offspring number and offspring quality, collapse into a single trade-off: division rate versus offspring (competitive) quality. Life history trade-offs have already been observed in single-celled organisms, such as yeast (*Saccharomyces cerevisiae*), in which slower growth rates (by mutations that are involved in ribosome biogenesis or in RNA polymerase) are associated with increased survival in challenging environments[7]. Below, we explore the presence of life history trade-offs and their ramifications for understanding and treating cancer.

Evolutionary life history theory can provide a useful framework for understanding the evolutionary selection pressures and adaptive strategies that govern the trade-off between increasing proliferation and survival for cancer phenotypes. Neoplastic cells are subject to evolutionary trade-offs with respect to resource allocation and growth constraints (as is the rest of nature). In this evolutionary competition, the 'proliferative hares' may reproduce rapidly but at the cost of increased mortality in adverse environments, whereas the 'quiescent tortoises' may proliferate more slowly but have the benefit of increased survival under stressful conditions, such as the administration of therapy. We propose that these trade-offs are crucial but poorly recognized components of cancer biology and that they have important implications for neoplastic progression and treatment. The mechanisms that underlie these trade-offs in normal and neoplastic cells are currently unknown, and it is has not yet been determined whether the characteristics of these trade-offs change during progression.

Various mechanisms may underlie these life history trade-offs. These mechanisms include those that are associated with trade-offs that are imposed by energy and time limitations, as well as trade-offs that are constrained by cell state or configuration. One probable energetic trade-off is that of ATP consumption by processes that promote proliferation versus processes that promote survival. Compared with non-resistant cancer cell lines, drug-resistant cell lines (that is, those that an have increased survival in toxic conditions) have approximately 50% less available ATP per cell[8]. Time limitations can also impose trade-offs, such as those between replicating DNA quickly (faster proliferation)

and replicating it accurately (indirectly increasing survival). Cells can also be subject to trade-offs among different states, as they cannot be, for example, in an autophagous state (which increases survival) and a proliferative state simultaneously.

The mechanisms that underlie the fast life history strategies of cancer cells include abrogation of cell cycle checkpoints, shortening of the G1 phase of the cell cycle, increasing the proliferation rate by suppression of DNA repair, use of fast (but error-prone) polymerases, activation of cell migration pathways and even the switch to glycolytic metabolism, which can facilitate increased proliferation[9] while generating a toxic acidic environment[10]. Alternatively, the mechanisms that underlie slow life history strategies include suppression of apoptosis, upregulation of efflux pumps, enhanced DNA repair, autophagy under starvation conditions, use of proofreading polymerases, remodelling of the tumour microenvironment, greater detoxification of reactive oxygen species (ROS)[11], and increased uptake and sequestering of resources, along with their efficient use through oxidative phosphorylation at the expense of proliferation[9].

In most cases, the exact characteristics of the trade-offs that occur between the mechanisms listed above have not yet been determined. However, some of these mechanisms probably involve antagonistic pleiotropy[12], in which a mutation that increases proliferation may decrease survival or vice versa. Antagonistic pleiotropy has been observed at the organismal level[13] and it seems to be instantiated by cell level characteristics, which include apoptosis and cellular senescence[14,15]. However, antagonistic pleiotropy probably also applies to cancer cells, which are subject to trade-offs between cell proliferation and survival that have emerged during somatic evolution. Because mutations that occur early in cancer progression may increase both survival and reproduction through inactivation of regulatory machinery (for example, inactivation of p53), we predict that antagonistic pleiotropy probably emerges later during progression (see below).

Life history theory and tumour ecology

Ecologists have found that populations in stable environments with limited resources evolve slow life histories[16] (this was historically called 'K-selection' after the carrying capacity term of the logistic model of population growth[17], although this terminology has lost favour). If resources are abundant and stable in the absence of predation (or other sources of high extrinsic mortality), the Malthusian law[18] will eventually lead to the population growing until it is resource limited, and therefore slow life histories will eventually be selected. Organisms with slow life histories tend to evolve larger bodies, better somatic maintenance and repair, chemical defences, mechanisms to survive environmental stresses, mechanisms to reduce the fitness of their competitors (in direct competition), slower metabolism, efficient uptake and use of resources, little dispersal and longer lifespans[16].

By contrast, environments with rapid and stochastic fluctuations in resource availability and/or high rates of extrinsic mortality (for example, predation) select for fast life histories (this was historically called 'r-selection' after the maximum growth-rate term of the logistic model[17]) that can exploit a temporary abundance of available resources and quickly repopulate following a disturbance in the environment. Organisms that evolve under fast life history selection tend to reproduce early and rapidly, deplete the resources of their local environment, migrate (to escape competition or depleted local environments and to find new regions where they can proliferate[19,20]), invest little in their own somatic maintenance, competitive capacity or their offspring and tend to die young[21]. There are exceptions to the general pattern of the trade-off between survival and reproduction, but these exceptions are typically due to trade-offs with other traits or constraints (for example, body size[22], dispersal constraints[23], age-dependent predation or mortality[24] and age-dependent competition[25]).

The terms r-selection and K-selection have lost favour because they are derived from a particular model of density-dependent population growth that might not apply to many biological systems of interest and that does not account for important selective forces such as competition and predation that may dominate the dynamics of many systems. In addition, the dynamics that result from variation in extrinsic and age-specific mortality rates are often more important than the population growth rate (r)[1,21]. We therefore use the terminology of fast and slow life history strategies, rather than the terms r-selection and K-selection.

Seed sizes in plants show several aspects of life history trade-offs: larger seeds occur because of greater investment of resources in survival, and they generally have a competitive advantage over smaller seeds. At low planting densities there is little correlation between the success of a species and its seed size. However, at high planting densities larger seeded plant species tend to be overrepresented when compared with smaller seeded plants[26], which shows the advantage that is derived from investment in quality over quantity in competitive, resource-limited environments.

Neoplastic cells have phenotypes that reflect many characteristics of fast and slow life history strategies. Indeed, all of the cancer 'hallmarks' (REFS 27,28) can be categorized as proliferation-promoting phenotypes, survival-promoting phenotypes or both (FIG. 1). Sustaining proliferative signals, evading growth suppressors and enabling replicative immortality are distinctive fast life history hallmarks, which enhance the capacity of cells to proliferate quickly to large numbers. Invasion and metastasis are other fast life history phenotypes, which are analogous to dispersal in organismal fast life history strategies. By contrast, evading immune destruction and resisting cell death are obvious slow life history hallmarks, which improve the ability of the cell to survive in challenging conditions. In addition, resource-limited environments would be expected to select for angiogenesis, which is analogous to 'niche construction' behaviour in slow life history organisms. Other hallmarks and enabling characteristics, such as deregulating cellular energetics and promoting tumour inflammation, may arise under fast or slow life history selection depending on the details of how these processes affect the cells. Early mutations may confer both proliferation and survival benefits by the disruption of regulatory machinery, so trade-offs between fast and slow life history characteristics of cells may not emerge until later in progression.

An evolutionary life history approach suggests that environments that are characterized by resource disturbance and high rates of cell mortality will probably select for fast life history proliferation-promoting hallmarks, whereas more stable but resource-limited environments will select for slow life history survival-promoting hallmarks. However, it is important to consider that these cell characteristics can in turn influence environmental conditions and could affect life history selection pressures; for example, angiogenesis may initially evolve under slow life history selection but could lead to selection for fast life histories upon a new abundance of (and probable fluctuations in) blood flow.

Tumour heterogeneity

Tumours are complex ecosystems that contain multiple evolving populations[29–33]. We know surprisingly little about the fundamental population biology parameters

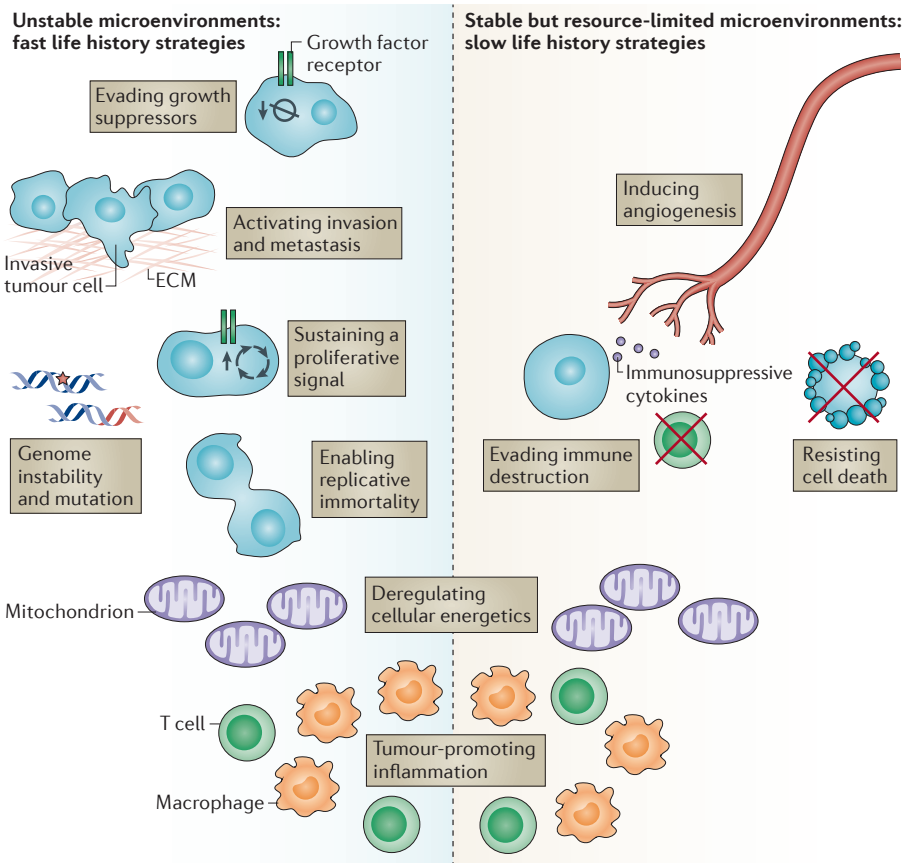

Figure 1 | **Hallmarks of cancer that are associated with life history selection.** Many of the hallmarks and enabling characteristics of cancer evolve under fast or slow life history selection. Environments that are unstable with regard to available resources and threats to cell survival — such as those that are characterized by wounding, variable blood flow or rapid changes in the availability of growth factors — will select for fast life history hallmarks (left panel). Environments that are characterized by less disruption but limited availability of resources, or by other population limitations such as immune predation, will select for slow life history hallmarks that increase cell survival or acquisition of resources (right panel). Some cancer hallmarks and enabling characteristics (shown between the two panels) are associated with both fast and slow life history strategies. ECM, extracellular matrix.

of *in vivo* neoplastic cells, which include death rates, proliferation rates, cell turnover rates, nutrient cycling, energetics and longevity. In many cases, it is not even clear what resources are limiting factors.

It is likely that both quiescent and proliferative phenotypes exist in a heterogeneous tumour population[34,35]. Tumours are mosaics of different microenvironments. Regions of low but stable resource availability (for example, hypoxia) promote strong competitor neoplastic cells (in the tumour interior), but regions of high or fluctuating resource availabilities (for example, at the edge of the tumour) allow the coexistence of cells that have traits for inefficient but rapid proliferation[36]. Life history phenotypes in cancers should generally be indicative of the availability of blood flow[37], the availability of resources, fluctuations in these availabilities, and extrinsic sources of mortality such as immune predation and chemotherapy.

The spatial heterogeneity in most tumours is apparent from variable enhancement of tumour regions in radiographic imaging after a contrast injection that increases visible differences among regions with differential blood flow and cell density (FIG. 2). In addition, temporal variation in blood flow to the same tumour region has been well documented in experimental systems. Blood flow and nutrients in tumours change from seconds to hours[38,39]. These temporal variations in resources should select for cells that proliferate quickly, deplete the resources of their environments and have higher rates of dispersal[19,20]. The coexistence of both stable and fluctuating microenvironments should both select for and permit the coexistence of fast and slow life history phenotypes within the same tumour[36]. Trade-offs between quick colonization (rapid division and migration into areas of unused resources) and effective competition (investment in survival) have been associated with the coexistence and evolution of slow and fast life histories in some ciliate protists[40]. Although heterogeneity in blood flow is the most obvious source of variations in extrinsic mortality and resources, other factors such as immune response, fibroblast infiltration, and hormone or growth factor availability may further contribute to divergent selective forces that are exerted on the life history phenotypes of neoplastic cells.

Cancer progression

The 'first law of ecology' (REF. 41) states that all populations have the capacity to grow exponentially under ideal conditions. In terms of life history theory, this selects for fast life history strategies[16]. The 'second law of ecology' recognizes limits to growth by stating that no population can grow exponentially forever without reaching some resource limitation; this would thus select for slow life history strategies.

Selection for life history strategies changes over both space and time as cells encounter resource limitations and gain the capacity to escape from those limitations. The fluctuating periods of selection for fast and slow life history strategies that accompany these resource limitations and escapes have specific characteristics that vary for different tissues and neoplasms. However, there are several resource limitations that are similar across many neoplasms (FIG. 3), although the exact order of these events probably varies.

Most epithelial tissues are subdivided into proliferative units. A mutant cell population may expand exponentially until it fills the niche of a proliferative unit. While the mutant cell population is constrained within this proliferative unit, there is selection for slow life histories that compete well for limited space and proliferative opportunities. If a new mutation allows a clone to escape a single proliferative unit — perhaps by stimulating crypt fission (which occurs in the stomach and intestine[32,42,43]) or through invasion into neighbouring proliferating units (which seems to occur in the skin[44]) — the neoplastic cell population can grow exponentially again. This will lead to a new phase of fast life history selection until the next resource limitation (caused by the epithelial tissue architecture) is reached.

As long as the epithelial tissue architecture is intact, a mutant clone that can escape its original proliferative unit is still constrained by the two-dimensional structure of an epithelial sheet, and it will eventually reach a new phase of slow life history selection.

Thus, proliferative units and the other constraints of tissue architecture are powerful tumour suppressors[45]. When their cellular phenotype becomes capable of three-dimensional growth, neoplastic cells can proliferate or survive without requiring attachment to the basement membrane (for example, by becoming resistant to anoikis or inducing autophagy[46]), as is seen in ductal carcinoma *in situ*[47]. Three-dimensional growth leads to a new phase of fast life history selection as neoplastic cells proliferate exponentially again. However, this exponential growth phase ends when the neoplasm begins to reach the limits of oxygen diffusion at a depth of approximately 2 mm (REF. 3). This leads to slow life history selection again, as cells compete for survival under resource-limited conditions, which are caused by the limits of diffusion from the existing capillary network.

Evolution of angiogenesis allows cells to escape from resource constraints and leads to a period of fast life history selection. However, an angiogenic tumour will typically reach space limitations that are imposed by organ membranes, which leads to slow life history selection again. After a neoplastic cell population escapes the final resource limitation by evolving the capacity for invasion and metastasis, it becomes difficult to manage clinically and often results in host death[48].

The clinical lethality of metastatic cancer may partly be because metastatic cells have evolved the capacity to break through resource constraints such as those shown in FIG. 3. When cancer cells colonize new tissues, they may be pre-adapted to quickly break through some resource constraints but not others. To the extent that the metastatic site affords similar environmental features and constraints as the primary site in which the cells initially evolved, the cells will not be held back by resource limitations and may therefore be able to maintain a fast proliferation rate in a new tissue. However, if the metastatic sites are sufficiently different from the primary site, the growth of metastases may be slowed because the cell populations may encounter novel resource limitations that they are not pre-adapted to overcome, such as different growth and survival factors in the microenvironment. It is not currently known whether the growth and survival factors in typical secondary sites are similar to those in the primary site, but this knowledge could help to explain why certain tumours are predisposed to metastasize to some sites and not to others. If these metastatic cells are able to grow at all in the new tissue, it is likely that they will be able to grow exponentially without encountering as many limitations as the cells in the primary tumour since they already have the capacity for three-dimensional growth, angiogenesis and invasion. This perspective may partially explain why metastatic cancer progresses quickly in some cases but slowly in others[28,49].

There is evidence that in some cases cancer single cell dissemination may occur prior to the primary tumour showing histologically recognized collective cell invasion[50]. Genetic analyses suggest single disseminated cells may derive from ancestral clones fairly early in progression[51]. These early dispersers may have evolved under early periods of fast life history selection (FIG. 3). Ecologists have recognized that there can be different mechanisms of dispersal, which respond to different selective pressures, even within the lifespan of an organism (for example, juvenile versus adult dispersal)[52]. We predict that early dispersing cells derive from lineages that have experienced less selection for increased proliferation and survival compared with cells that disperse later in progression, because early dispersers survive fewer phases of fast and slow life history selection. There should also be a lower probability of these cells being pre-adapted to breaking through all of the constraints on growing into clinically relevant metastases. Because the later dispersers have had more phases of fast and slow life history selection, they may have the capacity for faster proliferation, greater survival and phenotypic plasticity, which makes them more 'stem-like' compared with early dispersers (see below).

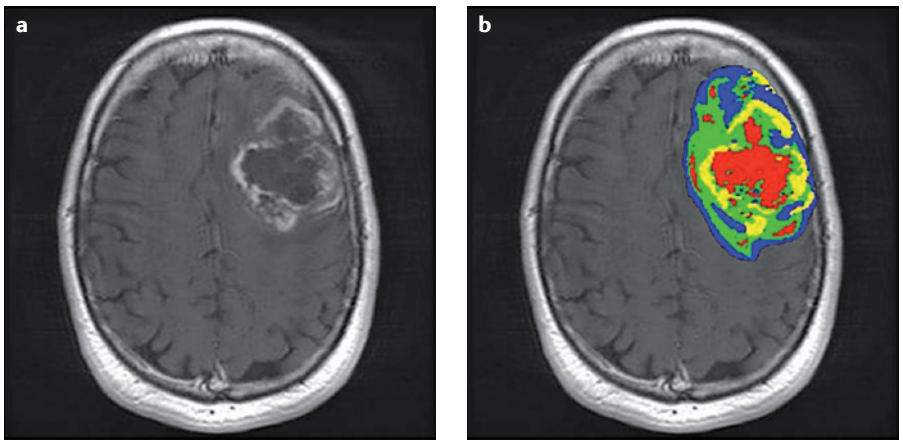

Figure 2 | **Tumour heterogeneity.** Both images show a magnetic resonance imaging scan of a glioblastoma after gadolinium injection at the H. Lee Moffitt Cancer Center, Tampa, Florida, USA. **a** | The grey-scale image is from a patient in The Cancer Genome Atlas glioblastoma dataset, and it shows the level of blood flow — white corresponds to the highest flow and black to little or no flow. Differences in the level of blood flow result in significant variations in the levels of many components of the tumour microenvironment, which include oxygen, glucose, acidic pH and serum-derived growth factors. **b** | An image that was created using methodology reported in REF. 110. Distinct intratumoural habitats are identified using combinations of images that correspond to vascular flow and cellular density, which reveal heterogeneity with regard to resource availability and space competition within the tumour (high blood flow and low cell density is shown in red; low blood flow and high cell density is shown in blue; high blood flow and high cell density is shown in yellow; low blood flow and low cell density is shown in green). Part **a** is reproduced, with permission, from REF. 110 © (2013) The Radiological Society of North America.

Life history trade-offs may emerge late

Our hypothesis is that, early in progression, mutations can improve both proliferation and survival without an apparent conflict (BOX 1; FIG. 4). This can be achieved by mutations that disrupt the regulatory machinery of the cell, which would otherwise limit the proliferation and survival of the cell. In normal cells, proliferation and survival are highly constrained to regulate the function (and ultimately promote the fitness) of the multicellular body of which they are a part. During the process of somatic evolution in neoplastic progression, cells may evolve improved proliferation and survival as they disrupt the regulatory machinery that would normally constrain them. However, these early mutations will not necessarily represent adaptations that maximize the fitness of the neoplastic cell. These early stage neoplastic cells retain many features that made them useful to the whole organism; namely, restrained proliferation, restrained nutrient uptake and metabolism, and additional cellular functions that aim to sustain

the physiology and homeostasis of the whole organism. Later in progression, cancer cells may become subject to trade-offs at the cellular level between survival and proliferation, as they can no longer improve one without sacrificing the other.

Trade-offs between proliferation and survival may lead to selection that favours extreme phenotypes, such as rapidly proliferating cells with poor survival abilities or apparently dormant cells that can survive extremely well (FIG. 4). The emergence of these trade-offs may even lead to selection for cells that can dynamically alter their phenotypes through epigenetic modifications on the basis of environmental conditions; for example, hypomethylation of oncogene promoters and/or hypermethylation of tumour-suppressor gene promoters may result in a proliferative phenotype, whereas signals of resource scarcity may induce a quiescent phenotype through hypomethylation of cell cycle inhibitor gene promoters and/or hypermethylation of pro-apoptotic gene promoters. In other words, there may be selection for cells that can dynamically alter their phenotypes to rapidly proliferate when resources are temporarily abundant but that become dormant when resources are scarce or when the environment is otherwise unfavorable[53]. If the capacity to dynamically switch from a fast life history to a slow life history phenotype provides a fitness advantage this may lead to selection for cells that are stem-like in their multipotent capacities.

Some evidence suggests that life history trade-offs may change during the course of progression. Slower proliferation rates have been observed in more advanced breast cancer cell lines compared with cell lines that have been taken from earlier stages of progression, but this decrease in proliferation seems to be accompanied by increased detoxification of ROS[11]. This apparent trade-off between proliferation rate and survival (via increased ROS detoxification) in advanced cancer may be explained by competition for NADPH, which is the limiting resource for both proliferation and detoxification[11]. Whether the emergence of trade-offs such as these is a fundamental feature of neoplastic progression is an unanswered question.

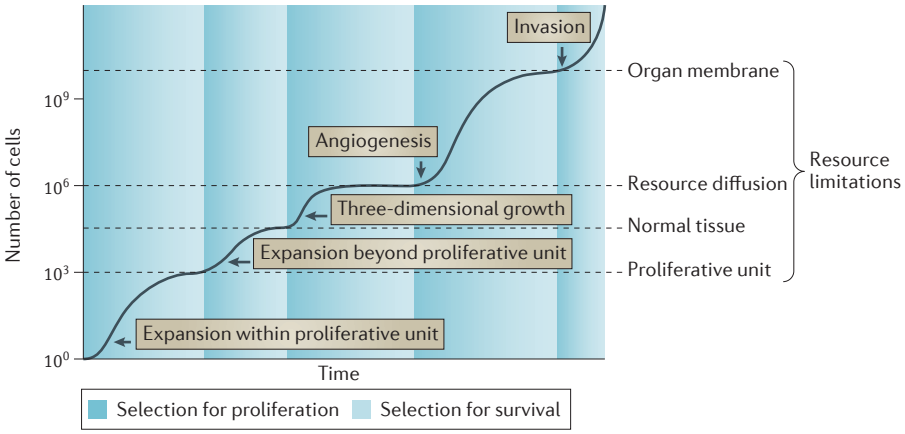

Figure 3 | **Resource limitation and escape during progression.** The 'second law of ecology' states that an exponentially growing population will eventually reach some limit to its growth. In neoplastic progression, there seem to be a series of limitations to the growth of neoplastic cell populations. During progression, the neoplastic cell population evolves mechanisms for escaping each limitation, which temporarily releases the neoplastic cell population with a burst of proliferation; this means that mutant cells with fast life history strategies have a competitive advantage (dark blue background). However, when those populations reach a new resource limitation, selection shifts from fast to slow life history strategies (light blue background); this means that the cells that have an advantage are those that can best compete, sequester resources and avoid death.

Cell plasticity and life history trade-offs

Although the concept of cancer stem cells remains controversial, there is clear evidence of phenotypic heterogeneity that can be regenerated from cells with markers of stemness[54,55]. One of the most puzzling aspects of cancer stem cells, and potentially a source of confusion in the literature, is their phenotypic plasticity. Cancer stem cells can survive and can show plasticity under challenging conditions[56]. Stem cells in normal tissues seem to be capable of generating a broad variety of proliferative phenotypes that range from rapid proliferation to dormancy[57,58]. There is increasing evidence that cancer stem cells are also capable of this broad variation in proliferation rates[59,60]; this may allow them to survive and maintain populations across diverse and stressful environmental conditions, and it may allow them to colonize new (metastatic) microenvironments. In other words, cancer stem cells seem to be capable of generating both a proliferative phenotype and a quiescent phenotype. This may indicate that cancer stem cells have the ability to conditionally produce cells with fast or slow life history strategies but with identical genetic heritage. However, the idea that life history trade-offs may drive cell plasticity is not dependent on the stem cell hypothesis. Even in the absence of stem cells, phenotypic plasticity may occur through epigenetic modifications[61] or through gene and non-coding RNA regulation[62].

Phenotypic plasticity is ubiquitous among organisms[5,63], and such changes in life history strategies are typically conditional on reliable environmental cues about the stability (or instability) of the environment. When there is a high probability that organisms will encounter various potential environments, they can evolve the capacity for state-dependent life history strategies ('reaction norms')[64]. Reaction norms allow organisms to adopt the phenotype that has the highest probability of maximizing their fitness in a particular environment. Intensely varying environments can induce a change in organismal life history strategies by providing cues indicating that a fast life history strategy would be more effective[65]. There are many examples of conditional life history strategies in response to predation, in which signals of increased predation lead to the organism adopting a faster life history strategy[66–68].

An example of phenotypic plasticity in response to environmental conditions is observed for the protist *Tetrahymena vorax*. This species is able to adopt two distinct morphotypes, which are called the microstome and the macrostome. The microstome consumes bacteria and small microorganisms. The macrostome consumes large prey such as other ciliates and protists. A microstome can morph into a macrostome in response to environmental cues of low bacterial abundance and high abundance of other protists. When the macrostome undergoes cell division, it can maintain its macrostome morphology or it can return to a microstome morphology, also in response to cues of its resource environment[69]. The ability of an organism to maintain distinct morphotypes and to be a generalist with a flexible 'behavioural' strategy leads to cells that are genetically identical but manifest a wide range of environmentally contingent traits. The molecular mechanisms that underlie this transition are unknown[70]. However, research on the phenotypic plasticity in social insects

Box 1 | **Trade-offs in trait combinations**

Evolution by natural selection promotes traits that may not have initially been constrained by trade-offs but that do eventually reach such a constraint. A 'fitness set' is defined as all combinations of aptitudes that an organism might have on the basis of its evolutionarily feasible traits[109]. When an organism is within its fitness set, natural selection can promote the improvement of multiple aptitudes. This will push the traits of the organism to the boundary of the fitness set (called the 'active edge'). When this occurs, it is not possible for the organism to evolve a trait value that simultaneously improves all fitness aptitudes. At the active edge, there is a trade-off among fitness aptitudes, and selection will move the trait along the active edge until the fitness-maximizing balance of aptitudes is achieved (FIG. 4). Trade-offs between survival and proliferation among cancer cells may be subject to the same constraints. We propose that early in progression neoplastic cells are within the fitness set and selection can simultaneously improve cell reproduction and survival. This leads to selection for neoplastic cells that move the population phenotypes towards the active edge (FIG. 4). Later in progression, after neoplastic cells have reached the active edge, they may be constrained by trade-offs between survival and reproduction or between competitive quality and reproduction. This may also lead to selection for plasticity or 'stemness' along the active edge, which can allow cells to dynamically optimize their proliferative or survival phenotypes for the conditions that they experience.

— honey bees (*Apis mellifera*) — provides evidence that both allelic variation and gene expression (probably from epigenetic modifications[71]) can produce colony members that have very different morphology and behaviour[72]. It has been suggested that life history traits contribute to the phenotypic plasticity among social insects (the developmental diet of female honey bee larvae determines whether they will become a worker bee or a queen bee)[73]. When such an adaptation occurs, the diversity of traits that is seen in the population emerges from a single flexible 'species' rather than from the coexistence of genetically distinct specialist species or clones[36]. Cancer stem cells may provide such a dynamic adaptation; their generalist strategy creates morphological diversity but not the genetic heterogeneity that would be found because of the coexistence of tumour cell lineages with specialist traits for either fast or slow life history strategies.

This concept is supported by experimental evidence that cancer stem cells can differentiate into diverse non-stem cell phenotypes when the cancer stem cells are engrafted into an immunocompromised mouse[74,75]. Recent evidence even suggests that non-stem-like cancer cells can dedifferentiate to a cancer stem cell phenotype[76], and that cancer stem cells can adopt various phenotypes that are associated with differentiation but can still maintain their stem-like properties[77].

The high mortality and disruption to resource availability that are characteristic of chronic wounding, dysregulated angiogenesis and the administration of cytotoxic therapies should provide reliable cues that signal neoplastic cells to develop fast life history phenotypes. By contrast, when resources are relatively stable but limited, which might be the case for non-angiogenic micrometastases, this may cause neoplastic cells to develop slow life history phenotypes. If these changes in the environment occur on a timescale that is shorter than the generation time of the neoplastic cells (which is probably the case for migratory cells) then cells that can change their phenotype will have an advantage over cells that have fixed life history strategies. This phenotypic change could occur by cells sensing environmental signals and adjusting their transcriptional programmes. Differentiation of cancer stem cells may be a result of conditional responses to the environment that parallel the ways in which organisms respond to environmental conditions[78].

If cancer cells use conditional life history strategies this might help to explain the apparent microenvironmental control of cancer cell phenotypes[79]. Several exciting studies have shown that in different microenvironments neoplastic cells can be driven towards a benign or a more aggressive phenotype. In other words, environmental cues may shift the phenotype of these cells from a fast life history phenotype to a slow life history phenotype or vice versa. Thus, inflammatory microenvironments, for example, may promote neoplastic progression[80–84] through environmental signals of high cell mortality that shift the strategy of the neoplastic cells to that of a faster life history. Because cell plasticity is thought of as an aspect of stemness, it is probable that the capacity for plasticity in cell life history strategies may be associated with stem-like cells. However, it is possible that a cell that does not carry stem cell markers could also shift life history strategies in response to environmental conditions.

Therefore, the apparent capacity of cancer stem cells to readily shift their phenotypes among different states on the basis of environmental cues may confer a fundamental evolutionary advantage on some neoplastic cell populations by allowing the cells to rapidly adapt to a wide range of environmental conditions. It is clear that the microenvironment has a crucial role in neoplastic progression[79]. However, if there is selection on neoplastic cells for the ability to adaptively shift phenotypes in response to environmental cues, this would be a novel component of cancer biology.

Life history characteristics may occur at the level of cell lineages or clones, as well as within a single cell; for example, a cell lineage with high levels of telomere maintenance may initially proliferate less rapidly, but it may result in a greater long-term survival of the clone. Similarly, a stem cell lineage that produces differentiated cell progeny may sacrifice rapid expansion of the number of stem cells in exchange for a survival benefit that is conferred through some function of the non-stem cells. We have previously shown that the conferring of survival benefit to the stem cell by non-stem cell progeny is a viable explanation for the existence of non-stem cells in neoplasms[85]. One mechanism of survival benefit may be analogous to the disposable soma hypothesis of ageing[86], which posits that ageing is a result of the high cost that is required to build and maintain a body that will be 'disposable' after viable offspring have been produced. It may be the case that a stem cell lineage can similarly enhance its competitive fitness by shunting misfolded proteins, deleterious mutations[45] and other cytoplasmic debris into a differentiating (ageing) daughter cell through an asymmetric division. Whether this occurs in neoplasms is unknown. Essentially, plasticity could be realized temporally by a cell switching its state, or spatially by a clone expressing multiple cell types. Spatial plasticity may facilitate the manifestation of complex life history strategies at the clonal level.

Treatments influence life history

Cancer therapy can influence the life history characteristics of tumours through selection (FIG. 5). A high-dose treatment that causes extensive cell mortality (for example, standard high-dose cytotoxic chemotherapy) and disruption of the environment may initially be fairly successful, and may result in the death of the majority of cancer cells. It is probable that high-dose therapies first select for slow life history characteristics; for example, in the presence of a cytotoxic agent, cells that have slow life history hallmarks may have a survival advantage over their competitors because of their survival strategies such as efflux pumps, increased drug metabolism,

increased DNA repair, increased cell size and inactivation of apoptotic pathways[87,88]. Interestingly (and unfortunately) this selection advantage may only be transient, because any surviving cells that have a fast life history strategy will have an advantage in the abundance of space and resources that follow the death of the sensitive population (this process is called 'competitive release' (REFS 89–91)) (FIG. 5a). By contrast, a treatment that limits and normalizes resource availability, or that otherwise controls the size of a tumour (for example, adaptive therapy[92]), may initially cause less tumour mortality but may select for cells that specialize in survival and competition, which have lower rates of proliferation; this would then allow long-term cancer control (FIG. 5b). Many targeted therapies are cytostatic[93] and are sometimes given in low doses and fairly continuously, which should limit the tumour size. In principle, this would cause some targeted therapies to select for cells with slow life history strategies. However, targeted therapies often cause massive cell death, and if they are given intermittently using only a few high doses then they are more like cytotoxic treatments. Dosing and treatment algorithms may have crucial effects on the evolution of cancer cells that could be harnessed to slow progression and the evolution of resistance.

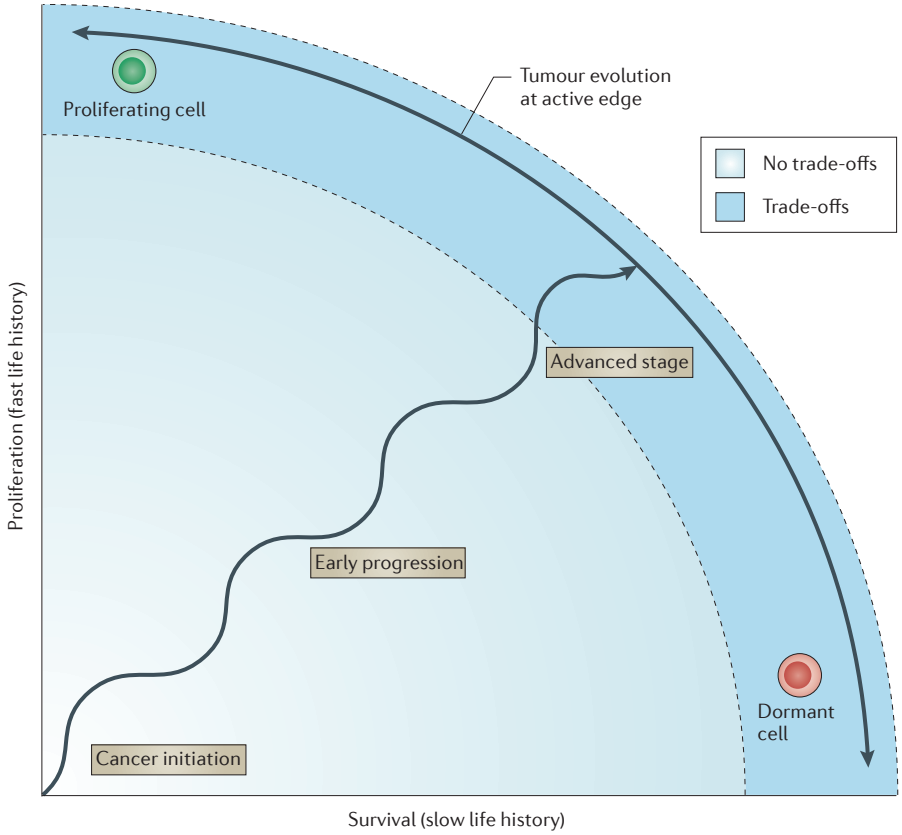

Figure 4 | **Trade-offs between proliferation and survival during cancer progression.** During progression, neoplastic cell lineages go through periods of selection for increased proliferation (represented by movement along the vertical axis) and increased survival (represented by movement along the horizontal axis), which might occur in phases as resource constraints are reached (selecting for survival) and broken through (selecting for proliferation). Early in progression, proliferation and survival can both increase without substantial trade-offs by the destruction of various regulatory systems within the cell that otherwise suppress those functions (BOX 1). Later in progression, the capacity of cells to proliferate and survive becomes limited by fundamental trade-offs, rather than by the regulatory machinery of the cell. Although some microenvironments may stably select for a particular point along this 'active edge' — and thereby lead to cells that have a specialized fixed life history strategy — temporal changes in the microenvironment or cell migration through different microenvironments may select for cells with phenotypic plasticity. In order to proliferate more quickly without sacrificing survival (or to improve survival without sacrificing proliferation), cells must be able to alter their phenotypes from reproduction-specialist phenotypes (for example, those of a proliferating cell) to survival-specialist phenotypes (for example, those of a dormant cell). This selection for phenotypic plasticity or 'stemness' (dark blue) later in progression may be explained by the fact that clones adopting a conditional phenotype that is subject to dynamic life history trade-offs can achieve higher fitness than those clones that are constrained to a phenotype with a fixed life history strategy.

Perhaps the most common selection event for cancer evolution is surgical excision. Surgery is meant to remove all of the tumour; it is essentially designed to be an extinction event. However, the surgeon may not remove all of the tumour — either inadvertently or owing to necessity if it is too extensive to be completely resected. In general, surgical resection targets macroscopically visible neoplastic cells and their neighbours. Neoplastic cells with increased motility that invade individually or in small groups will tend to survive surgery. In addition, the surgery can alter the local microenvironmental conditions in ways that are favourable or unfavourable to tumour growth; for example, an influx of inflammatory cells may increase the immune response to tumours or may promote tumour proliferation and motility. In either case, this is an interesting and mostly unexplored clinical opportunity for the application of evolutionarily-rationalized local or systemic therapy at the time of surgery, which could reduce subsequent tumour growth and might slow relapse; for example, this framework suggests that postoperative drugs that inhibit proliferative signals in the microenvironment could slow relapse (although this would probably occur at the cost of inhibiting surgical wound healing). In addition, surgery is probably a scattering event during which cancer cells can disseminate locally in the surgical field and systemically through blood and lymphatic vessels. There is a theoretical concern that cells with the highest probability of being 'shaken loose' from the primary tumour may also have properties that confer a greater probability of proliferation at a distant site. However, there is varied evidence for whether surgery increases the probability of metastases[94].

In addition, treatments may influence life history by creating environmental conditions that generate cues that may shift life history strategies of phenotypically plastic (stem-like) cells; for example, a cytotoxic treatment may induce a fast life history phenotype by exposing cells to cues of environmental disruption and high mortality that are then followed by opportunities for proliferation (FIG. 5c). A treatment that limits and normalizes resources might shift cells to a slow life history phenotype by exposing them to cues of high cell density and limited resources (FIG. 5d).

The effect of therapy on life history strategies of cancer cells raises the question of whether therapies can be designed to select or induce slow life history strategies. This may

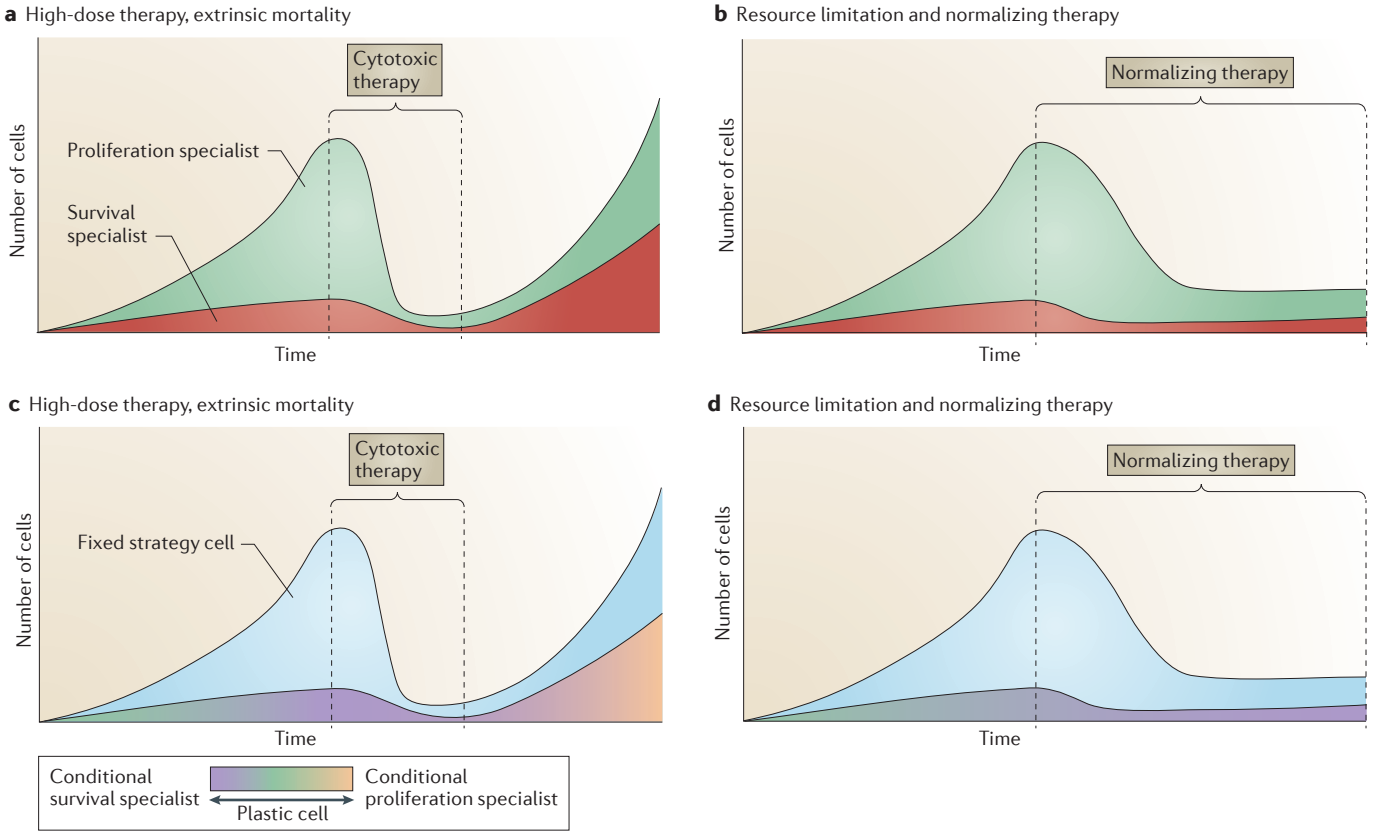

Figure 5 | **Effects of treatment on life history strategies.** Different treatments select for and induce different life history strategies. **a** | Traditional high-dose cytotoxic therapies cause high levels of cell mortality, which initially selects for survival specialists (light red) but, following this, if there is an abundance of resources and a paucity of competitors, proliferation specialists (green) gain an advantage, which may contribute to recurrence. **b** | A treatment that normalizes and limits resources results in selection for cells with slow life history strategies, which specialize in survival and competition (red); this treatment may facilitate long-term cancer control. A normalizing therapy would probably have to be applied indefinitely. **c** | Cells with conditional life history strategies may respond to cytotoxic therapies by shifting first to a survival phenotype (purple) and then to a rapidly proliferating phenotype (orange), which may lead to relapse. **d** | When exposed to a therapy that establishes a constant environment with limited but stable resources, cells that have conditional life history strategies may shift their phenotype to that of a slow life history that invests cellular resources in survival and competition (purple), which may allow long-term cancer control.

be a novel method for the long-term treatment of cancer, because (compared with fast life history strategies) slow life history strategies probably produce a more stable or more slowly expanding tumour that may have a lower probability of killing the patient. Thus, an explicit prediction of this approach is that therapeutic strategies that eschew high cell mortality and environmental change, and that instead promote a stable and predictable environment, and promote a relatively low extrinsic mortality, should lead to long-term cancer control. At least one experiment using an 'adaptive therapy' protocol in mice suggests that this is possible[92]. Unlike standard chemotherapy, adaptive therapy is designed to maintain a stable tumour size rather than to eradicate the tumour. Adaptive therapy uses a conditional algorithm that adjusts drug-dosing according to tumour burden. Mice with xenograft tumours of OVCAR-3 ovarian cancer cells were treated with carboplatin using both adaptive and standard therapy dosing schedules. The host mice in the adaptive therapy group were alive and had low tumor burden at the end of the 180 and 200 day studies, while the 'standard' high-dose chemotherapy-treated mice had to be sacrificed, owing to tumor burden, before the end of the study[92]. So far, these results have only been shown in one model system using one drug. In addition, experimental manipulations in mice designed to spatially homogenize the resources in a neoplasm resulted in a considerable suppression of metastasis[95,96]. It may also be possible to select for or induce slow life history strategies by maintaining a constant low dose of a drug (metronomic therapy)[97], particularly by using cell cycle-specific drugs that select against proliferating cells. However, the use of alternative dosing schemes is still at an early stage — a recent study of conditional intermittent therapy in prostate cancer showed equivalent overall survival compared with continuous anti-androgen therapy[98], which highlights the need for more research to determine the conditions under which adaptive therapy (and other conditional therapies) work. An understanding of the fundamental dynamics that drive life history evolution in neoplasms may help investigators to design more effective regimens for long-term cancer control.

Tumour dormancy

Many cancer therapies seem to result in residual but dormant neoplastic cells (minimal residual disease), which may lead to recurrence many years later[51,99,100]. In many cases, therapy itself selects for dormancy, by preferentially killing proliferating cells so that only the quiescent cells survive. Furthermore, dormancy may be an effective survival strategy for neoplastic cells when resources are limited. Proliferative cells may experience an internal phenotypic shift from a fast life

history strategy to a slow life history strategy in response to some extrinsic factors in the microenvironment[46,101]. In organismal evolution, lifespan increases among species that hibernate, possibly because of seasonal allocation of resources to reproduction (as opposed to using and requiring resources in all seasons, such as for annual plants)[102]. For neoplastic cells that are dormant following therapy, immediate proliferation will allow initial population growth (fast life history) but only if the environment has sufficient resources. Cells that delay proliferation (using a slow life history strategy) may be able to survive and maintain their overall quality when resources are scarce, but risk missing potentially successful cell division opportunities. Thus, cancer cell dormancy may represent an example of the life history trade-off between producing offspring as soon as possible and producing offspring later.

This implies that maintenance therapy in patients with minimal residual disease may extend the period of dormancy if the therapy maintains a limitation on resources for the cancer cells or if it provides other cues that maintain a slow life history phenotype; for example, anti-inflammatory drugs could possibly reinforce dormancy by maintaining a stable microenvironment and could inhibit pro-growth cues that are found in wound healing and in other inflammatory processes. Non-steroidal anti-inflammatory drugs (NSAIDs) have been found to prevent a wide variety of cancers[103], particularly oesophageal adenocarcinoma[104,105]. We have recently shown that NSAIDs can reduce the rate of mutation in Barrett's oesophagus (a pre-malignant condition) by an order of magnitude[106]. This large reduction in mutation rate per unit time may be due to a shift towards slower life history strategies of cells (a reduction in the rate of cell division), increased investment in DNA repair (a reduction in mutation rate per division) or reduced exposure to mutagens (for example, ROS).

If some cancer cells are able to conditionally shift their life history characteristics in response to environmental cues, it might also be possible to develop screening methods that could identify the presence of conditional life history cells, versus cells with fixed slow life history strategies, to predict the probability of recurrence. This may involve the detection of cancer cells using stem-cell markers, or using other markers of cells that have the capacity for plasticity in response to the opportunities and constraints in their microenvironments.

Conclusions

Life history theory provides a framework for understanding several puzzling aspects of cancer, including the mixture of rapidly proliferating and quiescent cells in the same tumour, the phenomenon of tumour dormancy followed by relapse, and the plasticity of so-called cancer stem cells. However, there has been controversy in the evolution and ecology literature over researchers using life history characteristics to classify organisms, rather than focusing on the types of selective pressures that shape a population[107,108]. A focus on the selective pressures that shape life history strategies in cancer suggests that there are opportunities for the development of new treatment regimens and prevention strategies that take life history evolution into account. The evolutionary life history approach suggests a potential strategy for prolonging the life of the host — not necessarily for eliminating the cancer but rather for achieving cure via long-term control.

C. Athena Aktipis, Amy M. Boddy and Carlo C. Maley are at the Center for Evolution and Cancer and the Department of Surgery, University of California San Francisco, 2340 Sutter Street, BOX 1351, San Francisco, California 94143–1351, USA.

C. Athena Aktipis is also at the Department of Psychology, Arizona State University, PO Box 871104, Tempe, Arizona 85287–1104, USA.

Robert A. Gatenby is at the H. Lee Moffitt Cancer Center, Tampa, Florida 33612, USA.

Joel S. Brown is at the Department of Biological Sciences, University of Illinois at Chicago, Chicago, Illinois 60607, USA.

Correspondence to C.A.A.
e-mail: aktipis@alumni.reed.edu

doi:10.1038/nrc3606
Published online 11 November 2013

1. Stearns, S. C. *The evolution of life histories* (Oxford Univ. Press, 1992).
2. Stearns, S. C. Trade-offs in life-history evolution. *Funct. Ecol.* **3**, 259–268 (1989).
3. Williams, G. C. Natural selection, the cost or reproduction and a refinement of Lack's principle. *Am. Nat.* **100**, 687–690 (1966).
4. Creighton, J. C., Heflin, N. D. & Belk, M. C. Cost of reproduction, resource quality, and terminal investment in a burying beetle. *Am. Nat.* **174**, 673–684 (2009).
5. Fabian, D. & Flatt, T. Life history evolution. *Nature Education Knowledge* **3**, 24 (2012).
6. Partridge, L. & Prowse, N. The effects of reproduction on longevity and fertility in male *Drosophila melanogaster*. *J. Insect Physiol.* **43**, 501–512 (1997).
7. Zakrzewska, A. *et al.* Genome-wide analysis of yeast stress survival and tolerance acquisition to analyze the central trade-off between growth rate and cellular robustness. *Mol. Biol. Cell* **22**, 4435–4446 (2011).
8. Broxterman, H. J. *et al.* Induction by verapamil of a rapid increase in ATP consumption in multidrug-resistant tumor cells. *FASEB J.* **2**, 2278–2282 (1988).
9. Vander Heiden, M. G., Cantley, L. C. & Thompson, C. B. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* **324**, 1029–1033 (2009).
10. Gatenby, R. A. & Gillies, R. J. Why do cancers have high aerobic glycolysis? *Nature Rev. Cancer* **4**, 891–899 (2004).
11. Jerby, L. *et al.* Metabolic associations of reduced proliferation and oxidative stress in advanced breast cancer. *Cancer Res.* **72**, 5712–5720 (2012).
12. Williams, G. C. Pleiotropy, natural selection, and the evolution of senescence. *Evolution* **11**, 398–411 (1957).
13. Leroi, A. M. *et al.* What evidence is there for the existence of individual genes with antagonistic pleiotropic effects? *Mech. Ageing Dev.* **126**, 421–429 (2005).
14. Campisi, J. Cellular senescence and apoptosis: how cellular responses might influence aging phenotypes. *Exp. Gerontol.* **38**, 5–11 (2003).
15. Ungewitter, E. & Scrable, H. Antagonistic pleiotropy and p53. *Mech. Ageing Dev.* **130**, 10–17 (2009).
16. Jeschke, J. M. & Kokko, H. The roles of body size and phylogeny in fast and slow life histories. *Evol. Ecol.* **23**, 867–878 (2009).
17. MacArthur, R. & Wilson, E. O. *The theory of island biography* (Princeton Univ. Press, 1967).
18. Malthus, T. R. *An Essay on the Principle of Population* (Johnson, 1798).
19. Aktipis, C. A., Maley, C. C. & Pepper, J. W. Dispersal evolution in neoplasms: the role of disregulated metabolism in the evolution of cell motility. *Cancer Prev. Res. (Phila)* **5**, 266–275 (2012).
20. Chen, J., Sprouffske, K., Huang, Q. & Maley, C. C. Solving the puzzle of metastasis: the evolution of cell migration in neoplasms. *PLoS ONE* **6**, e17933 (2011).
21. Reznick, D. & Bryant, M. J. & Bashey, F. r- and K-selection revisited: The role of population regulation in life-history evolution. *Ecology* **83**, 1509–1520 (2002).
22. Skutch, A. F. Life history of Longuemare's hermit hummingbird. *Int. J. Avain Sci.* **93**, 180–195 (1951).
23. Howe, H. F. & Smallwood, J. Ecology of seed dispersal. *Ann. Rev. Ecol. Systemat.* **13**, 201–228 (1982).
24. Promislow, D. E. L. & Harvey, P. H. Living fast and dying young: A comparative analysis of life-history variation in mammals. *J. Zool.* **220**, 417–437 (1990).
25. Ebenman, B. Competition between age classes and population dynamics. *J. Theor. Biol.* **131**, 389–400 (1988).
26. Turnbull, L. A., Rees, M. & Crawley, M. J. Seed mass and the competition/colonization trade-off: a sowing experiment. *J. Ecol.* **87**, 899–912 (1999).
27. Hanahan, D. & Weinberg, R. A. The hallmarks of cancer. *Cell* **100**, 57–70 (2000).
28. Hanahan, D. & Weinberg, R. A. Hallmarks of cancer: the next generation. *Cell* **144**, 646–674 (2011).
29. Gerlinger, M. & Swanton, C. How Darwinian models inform therapeutic failure initiated by clonal heterogeneity in cancer medicine. *Br. J. Cancer* **103**, 1139–1143 (2010).
30. Gillies, R. J., Verduzco, D. & Gatenby, R. A. Evolutionary dynamics of carcinogenesis and why targeted therapy does not work. *Nature Rev. Cancer* **12**, 487–493 (2012).
31. Greaves, M. & Maley, C. C. Clonal evolution in cancer. *Nature* **481**, 306–313 (2012).
32. Merlo, L. M., Pepper, J. W., Reid, B. J. & Maley, C. C. Cancer as an evolutionary and ecological process. *Nature Rev. Cancer* **6**, 924–935 (2006).
33. Nowell, P. C. The clonal evolution of tumor cell populations. *Science* **194**, 23–28 (1976).
34. van Diest, P. J., van der Wall, E. & Baak, J. P. Prognostic value of proliferation in invasive breast cancer: a review. *J. Clin. Pathol.* **57**, 675–681 (2004).
35. Kreso, A. *et al.* Variable clonal repopulation dynamics influence chemotherapy response in colorectal cancer. *Science* **339**, 543–548 (2013).
36. Orlando, P. A., Gatenby, R. A. & Brown, J. S. Tumor evolution in space: The effects of competition colonization tradeoffs on tumor invasion dynamics. *Front. Oncol.* http://dx.doi.org/10.3389/fonc.2013.00045 (2013).
37. Alfarouk, K. O., Ibrahim, M. E., Gatenby, R. A. & Brown, J. S. Riparian ecosystems in human cancers. *Evol. Appl.* **6**, 46–53 (2013).
38. Brurberg, K. G., Skogmo, H. K., Graff, B. A., Olsen, D. R. & Rofstad, E. K. Fluctuations in pO2 in poorly and well-oxygenated spontaneous canine tumors before and during fractionated radiation therapy. *Radiother. Oncol.* **77**, 220–226 (2005).
39. Cardenas-Navia, L. I. *et al.* The pervasive presence of fluctuating oxygenation in tumors. *Cancer Res.* **68**, 5812–5819 (2008).
40. Limberger, R. & Wickham, S. A. Competition-colonization trade-offs in a ciliate model community. *Oecologia* **167**, 723–732 (2011).
41. Turchin, P. Does population ecology have general laws? *OIKOS* **94**, 17–26 (2001).

42. Graham, T. A. *et al.* Use of methylation patterns to determine expansion of stem cell clones in human colon tissue. *Gastroenterology* **140**, 1241–1250 e1-9 (2011).
43. Greaves, L. C. *et al.* Mitochondrial DNA mutations are established in human colonic stem cells, and mutated clones expand by crypt fission. *Proc. Natl Acad. Sci. USA* **103**, 714–719 (2006).
44. Zhang, W. *et al.* UVB-induced apoptosis drives clonal expansion during skin tumor development. *Carcinogenesis* **26**, 249–257 (2005).
45. Cairns, J. Mutation selection and the natural history of cancer. *Nature* **255**, 197–200 (1975).
46. Kenific, C. M., Thorburn, A. & Debnath, J. Autophagy and metastasis: another double-edged sword. *Curr. Opin. Cell Biol.* **22**, 241–245 (2010).
47. Debnath, J. & Brugge, J. S. Modelling glandular epithelial cancers in three-dimensional cultures. *Nature Rev. Cancer* **5**, 675–688 (2005).
48. Etzioni, R. *et al.* The case for early detection. *Nature Rev. Cancer* **3**, 243–252 (2003).
49. Seliger, B. Strategies of tumor immune evasion. *BioDrugs* **19**, 347–354 (2005).
50. Rhim, A. D. *et al.* EMT and dissemination precede pancreatic tumor formation. *Cell* **148**, 349–361 (2012).
51. Schmidt-Kittler, O. *et al.* From latent disseminated cells to overt metastasis: genetic analysis of systemic breast cancer progression. *Proc. Natl Acad. Sci. USA* **100**, 7737–7742 (2003).
52. Debarre, F. & Gandon, S. Evolution in heterogeneous environments: between soft and hard selection. *Am. Nat.* **177**, E84–E97 (2011).
53. Wilting, R. H. & Dannenberg, J. H. Epigenetic mechanisms in tumorigenesis, tumor cell heterogeneity and drug resistance. *Drug Resist. Updat.* **15**, 21–38 (2012).
54. Clevers, H. The cancer stem cell: premises, promises and challenges. *Nature Med.* **17**, 313–319 (2011).
55. Magee, J. A., Piskounova, E. & Morrison, S. J. Cancer stem cells: impact, heterogeneity, and uncertainty. *Cancer Cell* **21**, 283–296 (2012).
56. Holzel, M., Bovier, A. & Tuting, T. Plasticity of tumour and immune cells: a source of heterogeneity and a cause for therapy resistance? *Nature Rev. Cancer* **13**, 365–376 (2013).
57. Li, L. & Clevers, H. Coexistence of quiescent and active adult stem cells in mammals. *Science* **327**, 542–545 (2010).
58. Wilson, A. *et al.* Dormant and self-renewing hematopoietic stem cells and their niches. *Ann. NY Acad. Sci.* **1106**, 64–75 (2007).
59. Biddle, A. *et al.* Cancer stem cells in squamous cell carcinoma switch between two distinct phenotypes that are preferentially migratory or proliferative. *Cancer Res.* **71**, 5317–5326 (2011).
60. Kusumbe, A. P. & Bapat, S. A. Cancer stem cells and aneuploid populations within developing tumors are the major determinants of tumor dormancy. *Cancer Res.* **69**, 9245–9253 (2009).
61. Sharma, S. V. *et al.* A chromatin-mediated reversible drug-tolerant state in cancer cell subpopulations. *Cell* **141**, 69–80 (2010).
62. Godlewski, J. *et al.* MicroRNA-451 regulates LKB1/AMPK signaling and allows adaptation to metabolic stress in glioma cells. *Mol. Cell* **37**, 620–632 (2010).
63. West-Eberhard, M. J. *Developmental Plasticity and Evolution* (Oxford Univ. Press, 2003).
64. Houston, A. I. & McNamara, J. M. Phenotypic plasticity as a state-dependent life-history decision. *Evol. Ecol.* **6**, 243–253 (1992).
65. Gurney, W. S. C. & Middleton, D. A. J. Optimal resource allocation in a randomly varying environment. *Funct. Ecol.* **10**, 602–612 (1996).
66. Ball, S. L. & Baker, R. L. Predator induced life history changes: Antipredator behavior costs or facultative life history shifts? *Ecology* **77**, 1116–1124 (1996).
67. Reznick, D., Butler, M. J. & Rodd, H. Life history evolution in guppies. VII. The comparative ecology of high and low predation environments. *Am. Nat.* **157**, 12–26 (2001).
68. Chivers, D. P., Kiesecker, J. M., Marco, A., Wildy, E. L. & Blaustein, A. R. Shifts in life history as a repsonse to predation in western toads (Bufo boreas). *J. Chem. Ecol.* **25**, 2455–2463 (1999).
69. Buhse, H. E. Jr & Williams, N. E. A comparison of cortical proteins in Tetrahymena vorax microstomes and macrostomes. *J. Protozool.* **29**, 222–226 (1982).
70. Ryals, P. E., Smith-Somerville, H. E. & Buhse, H. E. Jr. Phenotype switching in polymorphic Tetrahymena: a single-cell Jekyll and Hyde. *Int. Rev. Cytol.* **212**, 209–238 (2002).
71. Foret, S. *et al.* DNA methylation dynamics, metabolic fluxes, gene splicing, and alternative phenotypes in honey bees. *Proc. Natl Acad. Sci. USA* **109**, 4968–4973 (2012).
72. Fitzpatrick, M. J. *et al.* Candidate genes for behavioural ecology. *Trends Ecol. Evol.* **20**, 96–104 (2005).
73. Smith, C. R., Toth, A. L., Suarez, A. V. & Robinson, G. E. Genetic and genomic analyses of the division of labour in insect societies. *Nature Rev. Genet.* **9**, 735–748 (2008).
74. O'Brien, C. A., Pollett, A., Gallinger, S. & Dick, J. E. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. *Nature* **445**, 106–110 (2007).
75. Lapidot, T. *et al.* A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. *Nature* **367**, 645–648 (1994).
76. Gupta, P. B. *et al.* Stochastic state transitions give rise to phenotypic equilibrium in populations of cancer cells. *Cell* **146**, 633–644 (2011).
77. Taussig, D. C. *et al.* Leukemia-initiating cells from some acute myeloid leukemia patients with mutated nucleophosmin reside in the CD34$^-$ fraction. *Blood* **115**, 1976–1984 (2010).
78. Schlichting, C. D. Origins of differentiation via phenotypic plasticity. *Evol. Dev.* **5**, 98–105 (2003).
79. Bissell, M. J. & Labarge, M. A. Context, tissue plasticity, and cancer: are tumor stem cells also regulated by the microenvironment? *Cancer Cell* **7**, 17–23 (2005).
80. Bunt, S. K., Sinha, P., Clements, V. K., Leips, J. & Ostrand-Rosenberg, S. Inflammation induces myeloid-derived suppressor cells that facilitate tumor progression. *J. Immunol.* **176**, 284–290 (2006).
81. Bunt, S. K. *et al.* Reduced inflammation in the tumor microenvironment delays the accumulation of myeloid-derived suppressor cells and limits tumor progression. *Cancer Res.* **67**, 10019–10026 (2007).
82. Grivennikov, S. I., Greten, F. R. & Karin, M. Immunity, inflammation, and cancer. *Cell* **140**, 883–899 (2010).
83. Joyce, J. A. & Pollard, J. W. Microenvironmental regulation of metastasis. *Nature Rev. Cancer* **9**, 239–252 (2009).
84. Mantovani, A., Allavena, P., Sica, A. & Balkwill, F. Cancer-related inflammation. *Nature* **454**, 436–444 (2008).
85. Sprouffske, K. *et al.* An evolutionary explanation for the presence of cancer nonstem cells in neoplasms. *Evol. Appl.* **6**, 92–101 (2013).
86. Kirkwood, T. B. Evolution of ageing. *Mech. Ageing Dev.* **123**, 737–745 (2002).
87. Borst, P. Cancer drug pan-resistance: pumps, cancer stem cells, quiescence, epithelial to mesenchymal transition, blocked cell death pathways, persisters or what? *Open Biol.* **2**, 120066 (2012).
88. Gottesman, M. M., Fojo, T. & Bates, S. E. Multidrug resistance in cancer: role of ATP-dependent transporters. *Nature Rev. Cancer* **2**, 48–58 (2002).
89. Hibbing, M. E., Fuqua, C., Parsek, M. R. & Peterson, S. B. Bacterial competition: surviving and thriving in the microbial jungle. *Nature Rev. Microbiol.* **8**, 15–25 (2010).
90. Smith, V. H. & Holt, R. D. Resource competition and within-host disease dynamics. *Trends Ecol. Evol.* **11**, 386–389 (1996).
91. Wargo, A. R., Huijben, S., de Roode, J. C., Shepherd, J. & Read, A. F. Competitive release and facilitation of drug-resistant parasites after therapeutic chemotherapy in a rodent malaria model. *Proc. Natl Acad. Sci. USA* **104**, 19914–19919 (2007).
92. Gatenby, R. A., Silva, A. S., Gillies, R. J. & Frieden, B. R. Adaptive therapy. *Cancer Res.* **69**, 4894–4903 (2009).
93. Contractor, K. B. & Aboagye, E. O. Monitoring predominantly cytostatic treatment response with 18F-FDG PET. *J. Nucl. Med.* **50** (Suppl. 1), 97–105 (2009).
94. Coffey, J. C. *et al.* Excisional surgery for cancer cure: therapy at a cost. *Lancet Oncol.* **4**, 760–768 (2003).
95. Mazzone, M. *et al.* Heterozygous deficiency of PHD2 restores tumor oxygenation and inhibits metastasis via endothelial normalization. *Cell* **136**, 839–851 (2009).
96. Robey, I. F. *et al.* Bicarbonate increases tumor pH and inhibits spontaneous metastases. *Cancer Res.* **69**, 2260–2268 (2009).
97. Pasquier, E., Kavallaris, M. & Andre, N. Metronomic chemotherapy: new rationale for new directions. *Nature Rev. Clin. Oncol.* **7**, 455–465 (2010).
98. Crook, J. M. *et al.* Intermittent androgen suppression for rising PSA level after radiotherapy. *N. Engl. J. Med.* **367**, 895–903 (2012).
99. Aguirre-Ghiso, J. A. Models, mechanisms and clinical evidence for cancer dormancy. *Nature Rev. Cancer* **7**, 834–846 (2007).
100. Radich, J. P. & Wood, B. L. in *Leukemia and Related Disorders* (eds Estey, E. H. & Appelbaum, F. R.) 251–271 (Springer, 2012).
101. Lu, Z. *et al.* The tumor suppressor gene ARHI regulates autophagy and tumor dormancy in human ovarian cancer cells. *J. Clin. Invest.* **118**, 3917–3929 (2008).
102. Wilkinson, G. S. & South, J. M. Life history, ecology and longevity in bats. *Aging Cell* **1**, 124–131 (2002).
103. Rothwell, P. M. *et al.* Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet* **377**, 31–41 (2011).
104. Corley, D. A., Kerlikowske, K., Verma, R. & Buffler, P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. *Gastroenterology* **124**, 47–56 (2003).
105. Vaughan, T. L. *et al.* Non-steroidal anti-inflammatory drugs and risk of neoplastic progression in Barrett's oesophagus: a prospective study. *Lancet Oncol.* **6**, 945–952 (2005).
106. Kostadinov, R. L. *et al.* NSAIDs Modulate Clonal Evolution in Barrett's Esophagus. *PLoS Genet.* **9**, e1003553 (2013).
107. Parry, G. D. The meaning of r- and K-selection. *Oecol. (Berlin)* **48**, 260–264 (1981).
108. Mueller, L. D. Density-dependent population growth and natural selection in food-limited environments: The *Drosophila* model. *Am. Nat.* **132**, 786–809 (1988).
109. Levins, R. *Evolution in Changing Environments* (Princeton Univ. Press, 1968).
110. Gatenby, R. A., Grove, O. & Gillies, R. J. Quantitative imaging in cancer evolution and ecology. *Radiology* **269**, 8–14 (2013)

Acknowledgements

The authors thank A. Nedelcu, A. Caulin and A. J. Figuredo for thoughtful and thought-provoking discussions during the development of these ideas. This work was supported in part by Research Scholar Grant number 117209-RSG-09-163-01-CNE from the American Cancer Society, by US National Institutes of Health (NIH) grants F32 CA144331, R01 CA149566, R01 CA170595, R01 CA140657 and U54 CA143970, and by a grant from the McDonnell Foundation 220020270.

Competing interests statement

The authors declare no competing interests.

DATABASES

The Cancer Genome Atlas: https://tcga-data.nci.nih.gov/tcga/

ALL LINKS ARE ACTIVE IN THE ONLINE PDF