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Eco-evolutionary causes and consequences of temporal changes in intratumoural blood flow

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Abstract

Temporal changes in blood flow are commonly observed in malignant tumours, but the evolutionary causes and consequences are rarely considered. We propose that stochastic temporal variations in blood flow and microenvironmental conditions arise from the eco-evolutionary dynamics of tumour angiogenesis in which cancer cells, as individual units of selection, can influence and respond only to local environmental conditions. This leads to new vessels arising from the closest available vascular structure regardless of the size or capacity of this parental vessel. These dynamics produce unstable vascular networks with unpredictable spatial and temporal variations in blood flow and microenvironmental conditions. Adaptations of evolving populations to temporally varying environments in nature include increased diversity, greater motility and invasiveness, and highly plastic phenotypes, allowing for broad metabolic adaptability and rapid shifts to high rates of proliferation and profound quiescence. These adaptive strategies, when adopted in cancer cells, promote many commonly observed phenotypic properties including those found in the stem phenotype and in epithelial-to-mesenchymal transition. Temporal variations in intratumoural blood flow, which occur through the promotion of cancer cell phenotypes that facilitate both metastatic spread and resistance to therapy, may have substantial clinical consequences.

Tumours are dynamic ecosystems^{1,2} governed by diverse interactions of cancer cells with each other and with host stromal cells. All these cell populations depend on nutrients primarily delivered by blood flow in and around the tumour. In non-cancerous tissues, the organization of blood vessels is a marvel of biological engineering^{3,4} that ensures normal cells experience near constant delivery of substrate and removal of metabolites under physiological conditions^{4,5}.

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Author contributions

All authors researched data for the article, substantially contributed to discussion of the content, wrote the article and reviewed and/or edited the manuscript before submission.

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Blood flow within tumours, by contrast, is typically both spatially^{6–10} (FIG. 1) and temporally¹¹ (FIG. 2) heterogeneous. Evolutionarily, tumour angiogenesis represents a form of niche construction in which cancer cells promote a local vascular ecology (TABLE 1) that, by delivering nutrients and growth factors and removing potentially toxic metabolites, in turn promotes cancer cell proliferation. However, construction of tumour vascular networks is limited by Darwinian dynamics in which individual cancer cells are the units of selection¹² (TABLE 1). That is, in evolution of multicellular organisms, the whole organism is the unit of selection^{12,13}, and its individual cells contribute to and share its global fitness. As a result, evolution in multicellular organisms strongly selects for tissue-level cooperation among constituent cells to optimize organ function, thereby maximizing the fitness of the whole organism. These integrated cellular activities within a tissue allow formation of a robust and highly organized vascular network, which ensures survival and optimal function of all cells within the organ.

By contrast, in cancer evolution, individual cancer cells are the unit of selection and they must compete with each other for space and resources. Thus, Darwinian selection forces on each cancer cell promote optimized blood flow and nutrient supply only to that cell. As a result, the tumour vascular network is built entirely through local interactions between cells and their immediate environment, resulting in uncoordinated cellular production of proteins that regulate angiogenesis. These local interactions lead to highly constrained vascular networks¹⁴ in which cancer cells induce the growth of new blood vessels from the nearest available blood vessel (angiogenic sprouting) regardless of the size or flow capacity of the parental vessel (FIG. 2). In the absence of regulated vascular maturation, the network of new vessels remains unstable, undergoing continuous cycles of vessel growth and regression¹⁵. This vascular growth built solely on local interactions results in a haphazard spatial pattern and poorly controlled blood flow, which is analogous to the tangled irregular pathways in medieval villages and the chaotic traffic jams in modern cities (FIG. 2).

The environmental changes associated with heterogeneous intratumoural blood flow, in turn, act as a strong selection force driving evolution of local cancer cell populations (FIG. 3). Cellular adaptations to the consequences of chronic states of low and/or intermittent blood flow, including hypoxia and acidosis, have been extensively investigated^{16,17}. Here, we examine a slightly different question: what are the evolutionary consequences of temporal variations in blood flow that both result from and drive stochastic changes in environmental conditions, including changes in concentrations of oxygen, acid and growth factors? Organisms exposed to environmental fluctuations that are unpredictable in frequency and amplitude must develop adaptive strategies to both survive harsh environments and exploit opportunities during favourable conditions. In nature, the evolution and population dynamics in stochastic environments have been empirically and theoretically investigated^{18–20}. Successful adaptations include phenotypic plasticity²¹, population heterogeneity¹⁹, genetic assimilation¹⁸, bet-hedging^{22,23}, rapid patch depletion²⁴ and invasion of rich patches (nomadism)²⁵ (TABLE 1). We hypothesize that a number of cancer cell properties that contribute to invasion, metastases and therapy resistance arise as successful adaptive strategies to survive and proliferate within temporally unstable microenvironmental conditions.

Angiogenesis as niche construction

Fundamentally, normal organs are a collective of cells governed by control mechanisms that dictate the survival, reproduction, location and function of each cell and work in symphony to coordinate homeostasis²⁶. When the whole organism is defined as the Darwinian ‘unit of selection’^{12,13}, evolution promotes the organization of cellular societies to form well-functioning tissues such as highly structured vascular networks that can respond rapidly and effectively to changes in substrate demand and thus maintain cellular viability, function and repair in every region of the organ. The speed and flexibility of this vascular network are readily apparent in functional magnetic resonance imaging (MRI) studies showing increased blood flow and oxygen delivery within seconds of neuronal activation²⁷.

In tumours, each cancer cell is the unit of selection²⁸ because its proliferation is not controlled by local tissue signal but by the interactions between its phenotypic properties and local environmental selection forces (conditions). In the Darwinian environment of a cancer, each cell must compete with others for space and nutrients²⁹. This produces a very different dynamic, in which angiogenesis is promoted not by the whole organism but by individual cells solely for their own benefit. That is, each cancer cell acts to increase local blood flow and optimize its immediate environmental circumstances, but there is no evolutionary advantage to cancer cells for supporting vascular maturation³⁰ that would benefit other tumour regions.

The dynamics of tumour angiogenesis strongly resemble a well-studied ecoevolutionary process termed niche construction^{31,32} (TABLE 1), in which an organism modifies its environment to improve its own fitness — dams constructed by beavers, for example. Niche construction adds substantial complexity to the local eco-evolutionary dynamics^{33,34} by including an ‘ecological inheritance’ in the form of a persistent habitat that improves fitness of the progeny. Note, however, that beavers benefit only by producing dams for their own use and not for their neighbour’s use. Similarly, there is no evolutionary imperative for cancer cells to promote blood flow to other regions of the tumour. In fact, as these cells are competitors, there can be strong selection against such actions. Thus, cancer cells individually promote vascular growth in their vicinity by secreting paracrine angiogenic factors such as VEGF and angiopoietins^{14,35}. However, the evolutionary pressures of a substrate-limited tumour microenvironment within a tumour constrain cancer cells to invest no more than the minimum resources necessary to achieve the goal of vascular growth. Hence the resources needed to induce vascular growth towards the individual cell are rewarded by increased flow of nutrients and, to some extent, individual cancer cells must compete with each other in promoting angiogenesis. However, additional investment of resources to promote maturation and functionality of this network will provide little additional benefit to the cell and, in fact, will increase flow to other cancer cells in adjacent tumour regions, which are competitors. As a result, there is no Darwinian selection for individual cancer cells to promote vascular maturation or formation of a functioning network.

Thus, individually or through loose group dynamics, cancer cells compete for new blood vessels by secreting angiogenic factors^{36,37}. Because the resulting growth factor signalling

gradients are spatially constrained to the immediate vicinity of the tumour cell group, new vessels will arise from only the closest available vascular structure (FIG. 2). Construction of a circulatory network through entirely local interactions is similar to the haphazard organization of streets and alleys in growing but unregulated villages or modern cities where each new household simply connects to the nearest passageway regardless of its size or stability. The resulting vascular network lacks the hierarchical organization that efficiently delivers constant blood flow in normal organs (FIG. 2).

In turn, this disordered and unstable vascular network will produce complex, often chaotic, haemodynamics with ever-changing channels, eddies, back-flows and pooling of blood. With a sudden loss of flow, oxygen levels will decline rapidly, and levels of metabolic by-products such as acid and other metabolites will rise. Subsequently, rapid reversal of blood flow will bring nutrients and remove cellular by-products but at the cost of a burst of oxygen free radicals³⁸, with transient but potentially intense genotoxic stress^{39,40}.

In addition to the network's chaotic geometry, variations in cell density⁴¹, local pH, interstitial pressure⁴² and other environmental factors within tumour subregions can alter the blood vessel diameter and intratumoural pressure gradients, leading to substantial spatial and temporal variations in blood flow^{43,44}. The resultant changes in concentrations of oxygen⁴⁵ and metabolites produce striking and readily observable spatial variations^{41,46} in cancer cell densities (FIG. 1). By contrast, temporal variations in regional blood flow are far more difficult to demonstrate experimentally, and the importance of cyclic hypoxia for the metastatic dissemination of cancer cells was first proposed only in 2001 (REF⁴⁷). Importantly, these temporal dynamics are likely a 'zero sum game', in which reduction of blood flow and oxygen to one tumour region must be accompanied by a surge of blood flow and oxygen free radicals to an adjacent region. These multiscale spatial and temporal dynamics have been aptly characterized as 'waves and tides'^{48,49}.

Finally, while changes in levels of critical substrates such as oxygen are often emphasized in temporal fluctuations, we note that concentrations of serum-derived growth factors and hormones will also change with blood flow. Shifting patterns of cancer cell proliferation and death as well as activity of host immune and mesenchymal cells as a result of these changes in growth factor and hormone levels will create microenvironmental regions and time periods with diverse, often-transient opportunities and hazards⁵⁰.

Intermittent blood and oxygen supply

The earliest indications of temporally fluctuating blood perfusion and oxygenation come from 'dual-tracer' studies, wherein two different dyes are injected separately at different times into an isogenic murine head and neck squamous cell carcinoma model, SCCVII. Subsequent histology analysis of the tumour tissue revealed mismatches in dye distributions, providing evidence that perfusion across the tumour had changed during the time interval^{51,52}. This model was used because head and neck cancers are known to be hypoxic and thus radioresistant. It was, therefore, relevant to know whether perfusion, and hence hypoxia, was constant or intermittent^{53–55}. Such an approach has also been accomplished in vivo using MRI by injecting contrast agents at two different times. For example, in

melanoma xenografts, this approach revealed that the peripheral regions of the tumour had more perfusion variability^{56,57}.

More recent studies directly measured oxygenation in tissues (including tumours) with fluorescent and phosphorescent techniques at the microscopic scale. These investigations have documented both profound spatial heterogeneity in blood distribution and temporal stochasticity in tumour oxygenation^{40,58–60}. At a more mesoscopic level, gradient echo⁶¹ (GE)-MRI is sensitive to the presence of deoxy-haemoglobin^{62,63}. Longitudinal monitoring of tumours with GE-MRI has shown periodicities in oxygen levels (and presumably other substrates) ranging from seconds to minutes (waves) to hours (tides)^{64,65}. In some studies, these time-variant data can be subjected to sophisticated analytics to determine whether perfusion is periodic or stochastic⁶⁶. In such a study with colorectal cancer xenografts, it was observed that there were both periodic (systemic) and stochastic (local) oscillations and that the local, but not the systemic, oscillations increased with tumour size and vessel immaturity. Finally, direct in vivo measurements of tissue oxygen content with electron paramagnetic imaging⁴⁵ have enabled non-invasive visualization of spontaneous cycling hypoxia⁶⁷ in murine tumours.

Intratumoural evolution

Cancer cell evolution within tumours is often viewed as a process entirely governed by accumulating mutations⁶⁸. Heritable genetic changes are, indeed, critical in producing the phenotypic heterogeneity that influences survival and proliferation. However, the genetic paradigm tends to ignore two critical dynamics. First, transformed cells have access to all of the information stored in the human genome, which allows them to deploy molecular programmes from, for example, fetal development and wound healing, to adapt to environmental selection pressures of their tumour ecosystem. The sheer magnitude of this evolutionary potential is difficult to overstate. Consider, for example, the remarkable phenotypic diversity of domestic dogs — all of which emerged from evolutionary selection applied to a common wolf genome. Second, the fitness of any given clone is dependent on environmental conditions, which, within a typical tumour, vary over space and time. Furthermore, cancer cells are not simply passive components of the tumour ecosystem. Rather, as noted above, they are usually actively engaged in niche construction strategies, such as angiogenesis, to promote their own fitness. Importantly, however, the complex, coordinated functions necessary to generate complex, functioning vascular networks do not appear to be evolutionarily available for cancer cells as single units or necessarily fitness enhancing, as described above.

How many niches, how many species?.

A number of studies have found extensive molecular heterogeneity in cancer cells obtained from the same tumour⁶⁹. However, without understanding the environmental context of those cells and the phenotype expression of the observed molecular characteristics, the associated Darwinian dynamics cannot be assessed. That is, Darwin recognized the principles of evolution through observations that variations of beak morphology in different finch species matched those of the seeds within their island habitat⁷⁰. This logical

connection between evolved phenotypes and local environmental selection forces leads to a question not often asked in cancer biology: how many niches and how many cancer cell 'species' exist in a single malignant tumour?

In both preclinical⁷¹ and clinical cancer studies⁷², at least two coexisting cancer cell species and habitats have been identified. In tumour xenografts, in spontaneously arising tumours in genetically engineered mice and in histological samples from invasive breast cancers, cancer cells in the tumour periphery have been shown to predominantly adopt phenotypes characterized by high levels of proliferation, aerobic glycolysis (that is, anaerobic metabolism even in the presence of oxygen), motility and invasion^{73,74}. Alternatively, cancer cells in the tumour core tend to be angiogenic, slowly proliferative, nonmotile and maintain near normal levels of oxidative glucose metabolism⁷⁵. For example, in detailed spatial analysis of histological samples from invasive ductal carcinoma of the breast, carbonic anhydrase IX (CAIX), glucose transporter type 1 (GLUT1; also known as SLC2A1) and the proliferation marker Ki67 were upregulated at the tumour edge, which is consistent with an acid-producing, invasive, proliferative phenotype. Cells in the tumour core were 20% denser than those at the edge, and showed upregulation of CAIX, hypoxia-inducible factor 1 α (HIF1 α) and cleaved caspase 3, which is consistent with a more static and less proliferative phenotype. Similarly, vascularity was consistently lower in the tumour centre than at the tumour edges. Lymphocytic immune responses to tumour antigens tended to be increased at the tumour edge, whereas further away from the tumour periphery and deeper inside the tumour, they tended to be decreased⁷². Similar spatial patterns have been observed in melanoma and non-melanoma skin cancers⁷⁶ as well as in colon cancer⁷⁷. Furthermore, such edge versus core phenotypic variation is commonly observed in biological invasions, such as the cane toad expansion through Australia⁷⁸. Interestingly, manipulation of the tumour microenvironment can result in phase transitions favouring one species over another⁷¹.

Adaptive strategies

Evolution is often described as survival of the fittest. But 'fitness' is not a constant property of any given population. In fact, it is highly context dependent⁷⁹. A phenotype that is most fit in one microenvironment (for example, a desert) will rapidly become extinct when placed in another (for example, a rainforest). In an environment that is continuously changing, organisms with fixed phenotypes will experience a corresponding variation in fitness.

An environment that is nearly constant over time typically favours species that are highly specialized to these conditions. Even very harsh environments, if they are stable, can select for 'tolerator' (REF⁸⁰) species that grow slowly, are long lived and can avidly forage and retain available resources.

Temporal environmental fluctuations are often described as disturbance regimes⁸¹ in the ecological literature, and their impact on the evolutionary dynamics of local populations has been extensively investigated. Natural selection can never act on circumstances that have not yet occurred. But once an adaptive strategy has been selected, it can be maintained within the population to be deployed when similar stresses recur.

Thus, temporal fluctuations in environmental conditions generally promote phenotypes that can adjust to changing circumstances, often termed adaptive phenotypic plasticity⁸². Intermittent or alternating periods of favourable and unfavourable environmental conditions typically select for phenotypes that maximize the speed and efficiency with which available resources are converted into new offspring^{83,84} during the periods of ‘feast’. In periods of ‘famine’, species typically adapt with bet-hedging strategies⁸⁵ such as migration or dormancy, which maximize the probability of survival until conditions improve. These dynamics typically converge on two general adaptive strategies.

First, temporal uncertainty may promote a highly plastic phenotype⁸⁶ that can acclimate to diverse environmental circumstances. The adaptive success of phenotypic plasticity is governed by the amplitude and frequency of the environmental changes. For example, trees in northern forests can adapt in an orderly way to wide seasonal changes in temperature and sunlight provided those changes occur predictably (that is, cyclical) and over a time period that is slower than the time needed for the necessary phenotypic transitions⁸⁷. In cell biological terms, such species would shift from a quiescent state (in which autophagy is upregulated, for example) during bad times of nutrient scarcity to a highly productive state during good times of ample nutrient supply^{88,89}. This plasticity can also take the form of movement, as many bird and mammal species migrate (usually) north and south to experience relatively constant local environmental conditions. The Arctic tern, for example, migrates between the northern Arctic and southern Antarctica, in effect experiencing an ‘endless summer’⁸⁹.

When high amplitude environmental changes are stochastic rather than cyclical, phenotypic plasticity must become equally rapid to allow sudden shifts from survival to proliferative mode. Similarly, migratory plasticity can take the form of a nomadic pattern of movement, in which the species continuously moves away from harsh environments while detecting and invading more optimal locations. Unlike regular, migratory movement, nomadism can be effective when local fluctuations are extreme and unpredictable but at least partially coupled with changes in adjacent regions. In the zero sum game of tumour blood flow, in which decreased perfusion in one region must be matched by an increase in an adjacent site, increased motility and invasiveness of cancer cells continuously moving to optimal conditions would be evolutionarily favoured. A number of invasive properties of epithelial-to-mesenchymal transition (EMT)⁹⁰ and the role of oxygen concentration in regulating the transition⁹¹ suggest that these dynamics represent such an adaptive strategy.

Second, temporal variability can select for ‘speciation’, with coexistence of multiple phenotypes each optimally adapted to a subset of the conditions offered by the temporal fluctuations⁹². Here, each population proliferates very rapidly under its own optimal conditions but will typically undergo a rapid decline or stasis during adverse periods.

Adaptations and trade-offs

Cancer cells, like all evolving species in nature, must adapt to environmental conditions, including the stability or instability of those conditions. We can reasonably expect cancer cells to exhibit phenotypic properties that are adaptations to amplitude, frequency and

spatiotemporal autocorrelations of temporal variations in blood flow. In conjunction with average conditions^{93,94}, such variabilities will strongly influence the community of coexisting cancer cell species, their adaptations⁹⁵ and their capacity to persist and invade other environments^{96,97}.

A central concept in evolutionary adaptations to environmental selection forces is that of trade-offs. In an ideal environment with unlimited resources, there would be no constraint on continuous phenotypic optimization. However, when resources are limited, evolution requires that increased investment in one phenotypic property be accompanied by either increased resource acquisition or a corresponding decrease in resource allocation to another trait. This is perhaps most evident in the classic tradeoff between longevity (survivorship) and fecundity⁹⁸. Some organisms (field mice, for example) have a short lifespan and a high rate of death and reproduction, while others (humans and elephants, for example) have a longer lifespan but far fewer offspring. Similar life-history trade-offs have been recognized in cancer⁹⁹.

In responding to the stresses imposed by temporally fluctuating environments, cancer cells are similarly subjected to trade-offs among evolutionarily available strategies. These dynamics are complex, but observations in nature illustrate several common strategic trade-offs including phenotypic plasticity versus specialization, metabolic generalists versus specialists, ‘cream skimmer’ versus ‘crumb picker’ foraging and dispersal versus dormancy (TABLE 1).

Phenotypic plasticity: the cancer cell as a ‘jack of all trades’.

Some species adapt to varying environmental conditions through an increase in phenotypic plasticity (or reaction norm) so that the same genome can produce phenotypes that are well suited to, for example, both summer and winter conditions¹⁰⁰. In general, this strategy includes quiescence¹⁰¹ with intensive resource management during unfavourable environments and rapid shift to maximal energy acquisition and proliferation when conditions improve. Such phenotypic plasticity^{102,103} is readily observable in cancer cells as they transition to quiescence and autophagy in periods of harsh conditions¹⁰⁴ while converting rapidly to resource uptake and proliferation when the microenvironment is favourable¹⁰⁵.

Specialization strategies: cancer cell foraging and metabolism.

A central component of phenotypic plasticity in a changing environment is foraging — the acquisition and utilization of resources often framed as a competition between specialists and generalists^{106–108}. Generalists obtain nutrition from many sources in multiple habitats¹⁰⁹, while specialists are limited to only one or a few. For example, Darwin’s finches exhibit variation in beak size and morphology that is adapted to the local seed properties⁷⁰. However, coexisting ‘generalist’ ground finches overlap considerably in their choice of seeds, which can fluctuate seasonally and annually.

In stable environments or a stably fluctuating environment (that is, seasonal and diurnal variations), a specialist will typically outcompete a generalist. However, in an environment subject to wide and stochastic perturbations, generalists will typically dominate.

Interestingly, this selection for generalists may explain the frequently observed capacity of cancer cells to use a wide array of nutritional substrates^{110,111}.

Although rapid changes in substrates and metabolites are perhaps the most obvious and immediate consequence of temporal variations in blood flow, we note that these dynamics will also be found in local concentrations of serum-derived signalling molecules such as oestrogen, testosterone and growth factors. In some cases, this could select for cancer cell phenotypes that can survive and proliferate independently of these factors, leading to subpopulations in, for example, breast or prostate cancers that are resistant to hormonal therapy^{112,113}.

An alternative to a single highly plastic generalist phenotype is the coexistence of specialist phenotypes that are particularly suited to spatial or temporal variability in the abundance of a resource, such as the trade-offs between cream skimmer and crumb picker strategies^{114,115} (TABLE 1). The cream skimmer phenotype can move quickly or inexpensively between patches and harvest resources quickly but inefficiently. Thus, as nutrient availabilities vary in time and space, the cream skimmers locate, invade and proliferate in locally favourable patches¹¹⁶. At a given time, such patches have the greatest available resources relative to mean concentrations across all the patches. By contrast, crumb pickers lack this ability to move quickly. Even though slower in their nutrient uptake, crumb pickers compensate via their high foraging efficiency. By virtue of low foraging costs, they can deplete each patch to a very low abundance of resources¹¹⁷. When there are large spatial and temporal variabilities in resource concentrations, these strategies can coexist¹¹⁸ and may lead to spatial clustering of apparently disparate phenotypes in cancers¹¹⁹ (TABLE 1).

Specialization strategies: migration and nomadism.—In nature, generalist species often have larger geographic ranges and disperse more readily geographically^{120,121}. In the context of cancer evolution, generalist cancer cell types may be important for both local invasion and subsequent colonization¹²² of distant organs (that is, formation of metastases). The predicted evolutionary link between metabolic plasticity and dispersion is observed in both cancer invasion and metastasis^{75,123}.

Migration provides a common adaptation to seasonal fluctuations¹²⁴. By migrating, a bird avoids winter but at the additional energetic and injury costs of long distance flight¹²⁵. Resident birds forgo migration costs but must subsist on meagre food supplies and survive inclement weather. Like nature, we can expect to see in tumours the coexistence of motile and sedentary cancer cell types.

Because the temporal variations in environment are expected to be stochastic, we do not anticipate a migratory pattern will be commonly observed. However, we do anticipate that local temporal variations in blood flow will often have a zero sum quality, such that reduction of flow in one region is accompanied by a gain of flow in another region. This regional coupling will tend to select cancer cell motility that is nomadic, allowing the cells to move from one region to another along concentration gradients to maintain an overall richer environment. These adaptive dynamics may be observed in cancer cells during EMT, which increases cancer cell motility and invasiveness. The EMT programme can be triggered

by hypoxia^{126,127}, suggesting that it is, in part, a foraging strategy that permits localization and invasion into more favourable environmental regions during transient, spatially coupled increases and decreases in blood flow. Interestingly, these dynamics can become quite complex because as more and more cancer cells move away, the less motile cells will experience less competition and improved conditions even before a surge in blood returns. Interestingly, the reverse transition (mesenchymal-to-epithelial transition (MET)) has been observed in response to a normalization of local oxygen concentrations^{127,128}.

Conclusion

The uncoordinated niche construction mechanism of angiogenesis in tumours will, in most cases, lead to both regional and temporal variations in blood flow with corresponding fluctuations in environmental conditions. On the basis of the evolved adaptations to changing environments observed in nature^{129,130}, it is likely that stochastic microenvironmental conditions caused by disordered blood flow will select several cancer cell phenotypes. First, phenotypic plasticity allows cancer cells to proliferate rapidly in optimal conditions and, in adverse, potentially lethal environments, to quickly adopt a quiescent, autophagic phenotype that maximizes the probability of survival. Dormant¹³¹ or quiescent cancer stem-like cells are well recognized and thought to play a critical role in formation of metastases and treatment resistance^{132,133}. Second, cancer cells can become metabolic generalists and can obtain carbon, nitrogen, phosphate and other nutrients from a wide range of sources and mechanisms, including the scavenging of macromolecules from dead tumour cells^{134,135}. Such diversity¹³⁶ in cancer cell metabolism has been commonly observed and likely plays a critical role in tumour progression and metastasis¹³⁷. Importantly, this generalist strategy may select for phenotypes that are less dependent on certain growth factors such as oestrogen and testosterone by shifting their response to other serum-derived growth factors that are in better supply or by constitutively upregulating signalling pathways to become ligand independent. Alternatively, some cancer cells may evolve strategies to produce their own growth factors, as illustrated by upregulation of testosterone-producing cytochrome P450 17A1 (CYP17A1) during the development of castration resistance in prostate cancer¹³⁸. Third, cancer cells can adopt phenotypes that allow them to locate and move to the best available environment through high levels of motility and invasiveness — a phenotypic strategy likely observed during EMT in stressful environments and then reversed through MET when conditions are favourable. EMT appears critical for drug resistance¹³⁹ and formation of metastases.

The clinical consequences of time-dependent changes in blood flow are largely speculative but could well be important. Cancer cells described as stem-like as well as cells exhibiting aerobic glycolysis and EMT possess many traits that may have emerged as adaptive strategies to temporal environmental variation, including phenotypic plasticity, rapid cycling from quiescence to proliferation^{140,141}, metabolic reprogramming¹³⁷, therapeutic resistance¹⁴² and increased motility and invasiveness¹⁴³.

Furthermore, in animal experiments, cycling hypoxia has been found to increase both lymphatic and distant organ metastases^{47,144–146}, and formation of oxygen free radicals during re-oxygenation can promote progression of, for example, glioblastoma¹⁴⁷. Reduced

blood flow and environmental oxygen may contribute to resistance to radiation therapy and chemotherapy^{54,148–152}. The observed effects of fluctuating oxygen concentrations on individual cancer cells include increased genetic instability¹⁵³, defects in the mitochondrial apoptotic pathways¹⁵⁴, increased synthesis and release of angiogenic factors¹⁴⁶ and emergence of stem-like cell populations¹⁵⁵. Furthermore, temporal fluctuations in critical signalling molecules, such as oestrogen and testosterone, could select for hormone-independent phenotypes that serve as a reservoir population of resistant cells for subsequent hormonal therapy¹¹³.

Therapeutic strategies that reduce tumour vascularity have been extensively investigated^{156,157} and are now widely used. However, success of anti-angiogenesis treatments has been limited in part owing to evolution of tumour cell adaptive strategies that promote increased survival and invasion^{75,158}. More recently, investigators have proposed the somewhat counter-intuitive strategy of normalizing¹⁵⁹ tumour vascularity to, for example, improve drug delivery. We note that both strategies may be useful in cancer therapy, but neither can be employed successfully without a clear understanding and anticipation of the adaptive cancer cell strategies they will elicit.

Finally, we note the eco-evolutionary dynamics that govern temporal and spatial variations in blood flow are complex, multiscale and often nonlinear. As shown in FIG. 1, mathematical models that capture both the discrete (for example, cellular and blood vessel) and continuous (for example, spatial and temporal gradients in substrate, metabolites and growth factors) variables are necessary to fully elucidate these dynamics and predict the outcomes of therapeutic perturbations.

In summary, temporal variations in blood flow are a consequence of intratumoural eco-evolutionary dynamics that produce disordered and dysfunctional vascular architecture. In turn, stochastic variation in environmental conditions will likely select for cancer cell phenotypic adaptations that contribute substantially to tumour progression, metastatic disease and resistance to therapy.

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Fig. 1 | Multiscalar spatial and temporal variations in vascular flow lead to heterogeneous cell densities and properties.

a | A T1 post-gadolinium sequence from a magnetic resonance imaging (MRI) scan of glioblastoma shows spatially variable blood flow with high levels of contrast enhancement at the rim (arrows) and little to no flow in the central tumour regions. **b** | A T2-weighted sequence from the same MRI shows a corresponding increased signal in the low flow regions (arrows), indicating high fluid and diminished cell density. **c, d** | A haematoxylin and eosin-stained histological section from a clinical sarcoma shows high cell density in the upper half and almost complete necrosis in the lower half — highlighted in part **d**. The orange circle in part **d** indicates blood vessels in the midst of the necrotic region. The absence of viable cells next to these blood vessels suggests that the flow is temporary (literally a dry ‘streambed’). **e-g** | The complex spatial and temporal feedback pathways

involving evolving cancer cells and host vasculature can be framed mathematically as shown. A hybrid cellular automata model captures tumorigenesis (see REF⁷⁵ for details) by integrating both discrete elements (cells and blood vessels) and the continuous microenvironmental concentration gradients in substrate, metabolites and growth factors. In part **e**, the simulation considers infrequent vascular turnover. Vessels remained fixed for the entire simulation (6,756 ‘days’). The scale bar represents 400 μm . With a spatially and temporally stable environment, metabolically normal tumour cells (green cells) expand slowly into normal tissue. In part **f**, the simulation considers high vascular turnover and angiogenesis. Tumour perfusion is high but temporally unstable. In just 2,721 simulation days, the evolved tumour cells are mostly glycolytic (red), acid resistant (blue) or both (pink). Small regions of necrosis (black) are evident. In part **g**, the simulation considers high vascular turnover but only moderate angiogenesis. In 1,912 simulation days, the rapidly growing tumour is formed primarily by the glycolytic and acid resistant phenotype (pink), with extensive necrosis.

Fig. 2 |. The evolutionary constraints on tumour angiogenesis.

Angiogenesis in cancers must rely entirely on local interactions. Part **a** shows a well-organized vascular network of normal tissue, and part **b** shows a magnified region. In parts **c,d**, tumour growth at the edge of this tissue is initially supported by diffusion from the vessels in the existing network. Individual cancer cells farthest from the existing vessels become hypoxic (dark blue) and produce angiogenic factors. In parts **e,f**, this uncoordinated angiogenic signalling by individual cells produces vascular budding in only the closest vessels regardless of their size or flow capacity. In part **g**, progressive maturation of blood vessels results in an organized network and allows rapid and efficient haemodynamics, similar to traffic flow in a modern highway. In part **h**, tumour angiogenesis is more similar to the dynamics of villages or modern cities, in which each new household or small groups of households are constrained to build a connection with the nearest existing road or

passageway regardless of their size or capacity Part **g** image courtesy of Ivoha/Alamy Stock Photo. Part **h** image courtesy of Mitch Diamond/Alamy Stock Photo.

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Fig. 3 |. Key dynamics that result from variations in intratumoural blood flow.

Here, we summarize the role of environmental instability in key evolutionary properties of cancer cells as defined in the outer ring. A constant environment (inner ring), even if harsh, will select for stable phenotypes that are optimally adapted to local conditions and, therefore, tend to remain in place. By contrast, temporal variations in environmental conditions select for highly plastic phenotypes that can move from quiescence to rapid proliferation during periods of local feast or famine (middle ring). These adapted phenotypes are typically metabolic generalists — able to utilize a range of substrates including scavenging of macromolecules from dead and dying cells. Finally, because intratumoural blood flow is often coupled so that absence of flow in one region is accompanied by increased flow in an adjacent environment, these dynamics will select for motile, invasive phenotypes. Thus, tumour properties selected by spatiotemporal fluctuations in blood flow may promote formation of metastases and resistance to cytotoxic therapy.

Table 1 |

Events and mechanisms in cancer in terms of evolutionary ecology

Evolution term	Definition	Example of cancer equivalent
Evolution by natural selection	Evolution by natural selection has three critical components: heritable variation in the phenotypic properties, constrained proliferation owing to limiting environmental conditions and proliferation that is dependent on the interactions of the first two components	Temporal and spatial variations in the molecular and phenotypic properties of cancer cells
Ecology	The complex dynamic system resulting from the interactions and feedback pathways between organisms and the physical and organic components of their environment	The multiscalar interactions of cancer cells and normal cells within a region of tumour
Niche construction	The evolved capacity of organisms to modify their environment in a manner that improves their fitness	Examples of niche construction in cancers include angiogenesis and aerobic glycolysis producing an acidic local environment
Reaction norm	A change in the phenotype expressed by an organism as influenced by environmental conditions. These behavioural, physiological, morphological or epigenetic responses to circumstances may themselves be heritable	Phenotypic plasticity. Cells that exhibit EMT may represent the broadest reaction norm available to cancer cells
Cream skimmers	An organism or species that possesses a foraging pattern that is efficient but optimal at only relatively high levels of substrate. Usually, such species either move rapidly from one rich resource patch to another and/or profitably uptake resources when concentrations are high but are unable to do so when concentrations are low. They typically utilize abundant resources but stop foraging when the concentrations decline	Cells with normal levels of GLUT1 expression that function optimally at physiological levels of glucose and oxygen ⁶⁰
Crumb pickers	An organism or species that possesses a foraging pattern that is metabolically inexpensive and can obtain sufficient resources from environments in which substrates are sparse. Usually, such species move slowly between resource patches, depleting them to very low resource concentrations. They typically can profitably uptake resources even when those resources are rare	Cells that have high levels of GLUT1 expression and can continue to metabolize glucose even at low concentrations ⁷²
Unit of selection	Any population of organisms that experiences births and deaths, heritable variation and competition for resources and safety. Such a population can thus evolve by means of natural selection. A multicellular organism is ordinarily the unit of selection — each cell acts only when instructed by the host, leading to coordinated formation and homeostasis of tissues	Cancer can occur when cells transition to become the unit of selection so that their proliferation is dependent on their interactions with environmental conditions and independent of host control
Generalist versus specialist	A specialist is an organism who has a very high peak performance under optimal conditions but whose performance or aptitude declines rapidly as conditions change. A generalist may have a lower peak performance but maintains a high level of performance across a broad range of conditions. Specialists are highly adapted to a specific environment but survive poorly in other environments. Generalist can survive across a wide range of environments often via a broad norm of reaction (phenotypic plasticity). Often, stable environments favour specialists and highly variable environments favour generalists	Generalist cancer cells may, for example, switch from high levels of proliferation to quiescence, while specialist cancer cells may have a fixed proliferation rate
Adaptive strategy	A heritable trait that has evolved to increase or maximize the fitness of an organism given the properties of its environment	Cancer cell phenotype
Bet-hedging	An adaptive strategy whereby an organism sacrifices opportunities during the best of environmental conditions to buffer against the challenges of harsh conditions. The process is usually associated with organisms experiencing environmental extremes in time and space	Aerobic glycolysis, in which cancer cells maintain glycolytic metabolism even in the presence of oxygen (that is, the Warburg effect). Adopting this pathway instead of the more energy-efficient oxidative glucose metabolism is a trade-off for increased probability of survival if transiently decreased blood flow causes sudden and severe hypoxia
Tolerator species	Organisms adapted to environments that are harsh but relatively stable, such as deserts. They typically exhibit slow growth rates and are long lived, with diverse survivorship strategies, low phenotypic plasticity and high retention of available resources	Cancer cells defined as stem cells have phenotypic properties similar to tolerator species

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Evolution term	Definition	Example of cancer equivalent
Nomadism	A trait that allows organisms to adapt to stochastically varying environments by aggressively seeking and invading subregions of relatively favourable conditions	Because haemodynamic variations can be coupled so that decreased flow in one region can be accompanied by increased flow in an adjacent regions, motile, invasive cancer phenotypes such as EMT can serve as a successful adaptive strategy

EMT, epithelial-to-mesenchymal transition; GLUT1, glucose transporter type 1, erythrocyte/brain.