The evolution of the cancer niche during multistage carcinogenesis

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Abstract | The concept of the tumour microenvironment recognizes that the interplay between cancer cells and stromal cells is a crucial determinant of cancer growth. In this Perspectives article, we propose the novel concept that the tumour microenvironment is built through rate-limiting steps during multistage carcinogenesis. Construction of a ‘precancer niche’ is a necessary and early step that is required for initiated cells to survive and evolve; subsequent niche expansion and maturation accompany tumour promotion and progression, respectively. As such, cancer niches represent an emergent property of a tumour that could be a robust target for cancer prevention and therapy.

The paradigm that cancer is a cellular disease that is defined only by events within the genomes of cancer cells has given way in recent years to one in which cancer is viewed as an ecological disease involving a dynamic interplay between malignant and non-malignant cells. This shift redirects attention to the tumour microenvironment (TME), which encompasses signals, proteins and cells (such as immune cells and fibroblasts) present in the tumour mass that are necessary for tumour growth and progression. The contribution of the TME to malignant behaviours, treatment response and metastasis is an area of active research. The importance of the TME has been further underlined by the identification of the premetastatic niche. This concept is based on evidence from mouse models that established tumours release factors that can act on cells in distant organs to recruit bone-marrow-derived cells (BMDCs) that create an environment that is conducive to the survival and proliferation of newly arrived metastatic cells. Yet, is the generation of a hospitable environment restricted to metastasis? In this Perspectives article, we propose a broader concept: that the construction of a ‘cancer niche’ is an early and necessary step that is required for neoplastic cells to evolve towards a clinically relevant cancer. We are not suggesting that such niches pre-exist to facilitate cancer development and are somehow dormant or inactive in healthy individuals; rather, we propose that de novo cancer niche formation is the earliest stage at which non-malignant cells can be stimulated by the initiating carcinogenic insult and can support the survival of an initiated clone. In short, the development of a cancer niche is a prerequisite for tumorigenesis.

This Perspectives article uses the classical framework of initiation, promotion and progression to divide the stages of carcinogenesis. We propose that the evolution of the cancer niche can be divided into three phases: construction, expansion and maturation (Fig. 1). In brief, niche construction is a spontaneous interaction between activated stromal cells and normal cells that enables initiated (or transformed) clone survival. Niche expansion, which could be viewed as a ‘microenvironment’, generates secreted factors (such as chemokines, cytokines and exosomes) that remodel local tissue concurrent with initiated clone expansion and parallels tumour promotion (that is, the stage before tumour invasion). Recruitment of BMDCs as well as of resident cells (fibroblasts in particular) drives niche maturation from a nascent to an established TME, the composition of which is currently under intense research.

We propose that this concept of a dynamic and evolving cancer niche fundamentally changes how we view cancer. Our model postulates that cancer is as much a function of the successful construction of the niche as it is of the natural selection for specific mutations that enable cancer cell survival and proliferation. Consequently, tumour cell evolution in the context of a niche results in both normal and malignant phenotypes that cannot be understood solely in terms of epigenetic or genetic changes. Instead, these phenotypes represent an emergent property that requires comprehensive analysis of cell–cell interactions in the context of the entire construct.

The need for a cancer niche
In contrast to a physiological niche, such as the niche that functions to control haematopoietic stem cell (HSC) proliferation and survival1–4, a cancer niche would, by definition, evolve through steps that result in cancer cell survival, proliferation and gain of malignant potential. Is there any evidence of the need for such a process in carcinogenesis? Experiments in which cancer cells are exposed to a normal microenvironment — such as those by Barry Pierce, who injected carcinoma cells into developing embryos — resulted in the loss of malignant behaviour, which indicates that the environment in which cancer cells exist influences their behaviour, despite the presence of genetic and epigenetic alterations. Likewise, combining cancer cells with normal mesenchymal results in varying degrees of cancer cell differentiation5–9, and cancer cells can form muscle cells when transplanted into normal muscle10. Moreover, G.H. Smith and colleagues11,12 provided a striking demonstration of the capacity of normal tissue to revert a malignant phenotype. Pluripotent human embryonal carcinoma cells and human metastatic, non-metastatic and metastasis-suppressed breast cancer cells produced normal epithelial progeny without tumour formation when injected into a regenerating mammary gland microenvironment in vivo11,12. These experiments and others13,14 show that cancer cells carrying sufficient mutations to confer neoplastic potential can be suppressed by normal tissue. Therefore, one can infer that mutations in cancer cells alone are not able to induce tumour growth, and that active changes in the surrounding tissue cells must be essential for the clinical development of cancer.

Consistent with this idea, the initiation of tumorigenesis by the expression of an oncogene or deletion of a tumour suppressor gene in mouse tissues is remarkably inefficient at generating cancers. From a cancer genome perspective, this is often attributed to the need for additional sporadic genetic alterations. Considering the host stroma as a necessary participant provides another explanation for this apparent inefficiency: the juxtaposition of initiated cells with host cells that favour survival, proliferation and genomic evolution is stochastic and rare, which limits the further evolution of transformed cells. Thus, in a young, healthy individual, a cancer niche develops by chance, not by intrinsic capacity. It is conceivable that, occasionally, the initial transforming event might result in signals that actively recruit a compatible host cell partner. But more often than not,
host processes (such as ageing and chronic inflammation) that are associated with cancer development increase the likelihood of such events coinciding.

**Construction of a cancer niche**

How are normal cells involved in the earliest steps of cancer development, when we argue that the cancer niche is formed? Here, we consider evidence that carcinogenesis is initiated when interactions between a genetically initiated cell and particular host cells in the developing niche facilitate survival and malignant behaviour.

One example of niche construction that is induced by oncogene expression is that of transgenic KRAS mutations; the key downstream targets of many of these mutations are cytokines and chemokines\(^1\). In particular, crucial events are likely to be the upregulation of chemokines, such as interleukin 8 (IL-8)\(^1\) and CXCL1, and cytokines, such as granulocyte–macrophage colony-stimulating factor (GM-CSF) and IL-6. They in turn activate and remodel stromal cells that promote progression to dysplasia\(^1\). In this case, the products of the initiating mutation elicit the construction of a precancer niche.

A second example comes from experimental models of chemical carcinogenesis. In skin carcinogenesis, initiation with 7,12-dimethylbenz(α)anthracene (DMBA) is followed by 12-O-tetradecanoyl-phorbol-13-acetate (TPA), whereas in colorectal carcinogenesis, initiation with azoxymethane (AOM) is followed by dextran sodium sulphate (DSS)\(^1\). A key piece of the two-stage carcinogenesis strategy is that each exposure alone is insufficient to generate tumours. Carcinogens are clearly capable of initiating — presumably by genomic change — the target cells, which remain ‘latent’ until the tissue is treated with a promoter. Classically, this requirement for a tumour promoter is explained by invoking the need for proliferation, which then expands the initiated cells. We propose an alternative explanation: chemical promoters recruit or induce host stromal cells that can partner with the initiated cell, forming a precancer niche. One action that is common among chemical promoters is that they induce substantial inflammation, either primary inflammation as occurs with TPA treatment, or inflammation that is secondary to injury as occurs with DSS treatment; thus, this tumour promotion can usually be blocked with anti-inflammatory therapies. These experimental models reflect the clinical observation that cancer often arises in the setting of repeated injury (such as tobacco carcinogens) or chronic inflammation (such as that induced by chronic *Helicobacter pylori*-mediated gastritis)\(^1\). We speculate that chemical promoters enable niche construction, which supports the proliferation of the initiated clone. This hypothesis is experimentally testable by using strategies to silence or block particular stromal phenotypes.

A third example is that of physiological conditions that may also modulate the frequency with which initiated cells can construct a permissive stromal environment. Tlsty and colleagues\(^2\) investigated the association of high mammographic density with increased risk of breast cancer. They found that stromal tissue from women with dense...
Mice that have been irradiated and subsequently transplanted with non-irradiated, oncogenically primed mammary epithelial cells develop aggressive tumours with a shorter latency than recipient mice that have not been irradiated. Given that the mammary epithelium was not irradiated in these experiments, the acceleration of tumorigenesis results from direct radiation effects on the microenvironment. This acceleration depends on TGFβ1 (REF. 31), through either stromal remodelling or low-grade inflammation. Similar effects have been noted in muscle: tumour cells transplanted into normal muscle differentiate into functional muscle, but give rise to tumours when transplanted into irradiated muscle. Likewise, irradiating mice that have neuronal-specific mutations in the Hedgehog receptor, patched homologue 1 (Ptc1), increases the incidence of medulloblastoma, even when the brain is shielded from ionizing radiation. In each of these studies, the cells giving rise to the cancer were not irradiated, so only the irradiated stroma is modulating tumour incidence. These observations are consistent with the notion that complete carcinogens increase niche construction. One mechanism might be through the contribution of immune cell phenotypes to cancer niche construction. An intriguing example that was shown by Wright and colleagues is that macrophages in irradiated mice produce signals that include CD95 ligand, tumour necrosis factor-α (TNFα), nitric oxide and superoxide. Interactions between these irradiated macrophages and non-irradiated bone marrow cells generates DNA damage, as shown by chromosomal instability in target cells. The juxtaposition of activated macrophages and initiated cells, each induced by radiation, could lead to increased DNA damage and genomic instability, independently of mutations that already exist in the initiated cells.

**Potential signals.** Essential signals in these early stages of the cancer niche are currently unknown but probably include both stromal-cell-derived factor 1 (SDF1, also known as CXCL12) and TGFβ. TGFβ seems to be an important mediator of niche remodelling throughout cancer progression. TGFβ polymorphisms that affect its activity are associated with cancer susceptibility in a complex manner. Conditional inactivation of the TGFβ type II receptor gene in a subset of fibroblasts that express fibroblast-specific protein 1 (FSP1) leads to the rapid development of neoplasia in the prostate and forebrain. Conditional deletion of this receptor also results in defective mammary ductal development and accelerated neoplastic progression, in part owing to increased stromal production of hepatocyte growth factor (HGF) and TGFβ polymorphisms. Consistent with this, human fibroblasts that have been engineered to overexpress TGFβ or HGF promote the development of histologically dysplastic lesions from normal human mammary epithelial cells when co-implanted into nude mammary glands. Together, these studies underscore the importance of TGFβ in modulating the stromal–epithelial interface during the earliest stages of oncogenesis.

Recent findings on tumour-generated exosomes — which are 30–90 nm vesicles that are released from the cell when multi-vascular bodies fuse with the plasma membrane — have changed how we view communication between tumours and organs. Importantly, exosomes, which contain proteins and nucleic acids that can dramatically modify the recipient cells, can clearly act systemically and seem to have a major role in the crosstalk between initiated cells and host tissues. In fact, increasing evidence demonstrates that tumour-secreted exosomes profoundly regulate the immune response and the haematopoietic system in general, including lineage-specific differentiation of bone marrow precursors, dendritic cell function and transference of molecules. Altered exosome production or composition can alter the fate of nearby cells and thus could contribute to early cancer niche formation by mobilizing potential niche partners. Exosomes are implicated in stress responses to injury, which have long been associated with cancer development. Several studies have linked TGFβ in exosomes to immune modulation, but a recent study also reported that TGFβ in exosomes contributes to remodelling of the TME by stimulating the differentiation of fibroblasts into myofibroblasts, which we speculate could contribute to niche construction or expansion.

**Niche expansion.** As the initiated clone expands and acquires more mutations, the activation of oncogenic signalling pathways might also trigger niche expansion, thus leading to the recruitment of additional inflammatory cells and reprogrammation of the stroma. Initiated cells are not readily identified in situ, but further progression to the stage of dysplasia, which is the earliest...
histological evidence of neoplastic potential, produces systemic signals that lead to profound reprogramming of the bone marrow stroma and mobilization of cells that can expand the cancer niche. Signals from the nascent niche can act both systemically and locally to expand the niche during progression from dysplasia to carcinoma in situ.

**Immune cells.** Tumour-promoting agents, such as TPA, stimulate the recruitment of immature myeloid cells (IMCs) to incipient tumour sites in chemical-carcinogen-treated skin. After a single TPA application, IMCs are mobilized from the bone marrow and increase ~3.5-fold in number in the peripheral blood, followed by recruitment to the skin, and these cells persist in models of two-stage carcinogenesis. In addition, these IMCs induce a greater recruitment of α-smooth muscle-actin-positive (αSMA⁺) fibroblasts, 20% of which are bone-marrow-derived. These bone-marrow-derived cells are mainly derived from the mesenchymal stem cell (MSC) lineage. MSCs normally generate αSMA⁺ myofibroblasts in order to maintain their own niche within the bone marrow: both cell types are recruited to tumours. During tumorigenesis, both the MSCs and the αSMA⁺ daughter cells are recruited to the expanding tumour niche, which promotes further tumour growth and malignant progression. Thus, the second phase of niche evolution, niche expansion, involves the recruitment of bone-marrow-derived myeloid cells, MSCs and myofibroblasts that together probably enable progression. Interestingly, MSCs in the precancer niche may be recapitulating their physiological role to establish the haematopoietic stem cell niche, in part by reciprocal regulation by myofibroblasts.

A study from Lyden and colleagues first identified myeloid progenitor cells as necessary components of the TME in 2001, and recent studies have shown that they also participate in the formation of a premetastatic niche. Studies of many carcinogenesis models have clarified that innate immune responses, particularly the recruitment of IMCs, are crucial during the initial steps of cancer. IMCs are defined as a heterogeneous population of CD11b ‘GR1⁺’ cells that include both granulocytic and monocyte precursors and constitute a large proportion (>30%) of nucleated bone marrow cells. Typically, they are less abundant in the circulation and rare in most peripheral tissues and organs. However, their numbers are markedly increased in cancers, where they also acquire immune-suppressive properties and thus have been described by some as myeloid-derived suppressor cells (MDSCs). Many models of carcinogenesis, IMCs are among the first cell types that are recruited to a nascent TME. For example, IMC levels are increased in the skin within 6 hours of exposure of the skin to TPA. In mouse models of colorectal cancer, repeated doses of AOM (that is, >3 doses) are needed to both recruit IMCs to the colon and induce colon tumours, thus indicating a tight link between these two processes. Transgenic models of gastric cancer (mice that overexpress H⁺/K⁺-ATPase and IL-1β or oesophageal cancer (conditional p120 catenin knockout mice) are also notable for the early recruitment of IMCs to the incipient tumour sites, before any other changes in the mucosa. Genetic alterations, such as knockout of histidine decarboxylase, that led to an increase in circulating IMCs also led to a more rapid induction and growth of cancer cells at multiple sites (such as the colon, skin and stomach) in response to carcinogens. Thus, the recruitment of IMCs to the precancer niche is probably one of the earliest changes of cancer formation.

Although IMCs are probably necessary, they are not sufficient for cancer: exposure of the skin to TPA alone does not induce skin cancer, neither is DSS-induced colitis sufficient for colon cancer initiation. Unlike resident tissue macrophages (which are not bone-marrow-derived), IMCs are short-lived and typically mature to monocytes and neutrophils and then seem to diminish. Thus, a long-lasting, and possibly permanent, effect of niche formation may be required to stabilize the IM phenotype locally. With a complete carcinogen, such as infection by Helicobacter species, levels of myeloid cells remain increased in the circulation and at the tumour site. Eventually these IMCs result in the recruitment of fibroblasts and the induction of angiogenesis, together these events establish a TME that further promotes tumour cell proliferation and progression.

Interactions between adaptive immune cells and transformed cells also determine cancer progression. To examine the link between chronic inflammation and skin cancer, Coussens and colleagues used a transgenic mouse model that expresses the human papillomavirus type 16 (HPV16) early region genes under the control of the keratin 14 (K14) promoter. In this study, B lymphocytes did not infiltrate skin tumours, but were required for tumor development because of their production of immunoglobulins. Indeed, crossing the K14–HPV16 mice with Rag1⁻/⁻ mice, which lack mature B and T cells, blocked leukocyte recruitment and chronic inflammation that generate pro-angiogenic factors, an activated vasculature and hyperproliferation of oncogene-expressing keratinocytes. Transfer of either B lymphocytes or serum from K14–HPV16 mice effectively restored the chronic inflammation and malignant progression in K14–HPV16/Rag1⁻/⁻ mice. Importantly, all of these changes occurred in the premalignant phase of tumour development.

**MSC and fibroblast contributions.** Several studies suggest that abnormal fibroblasts can induce tumour promotion. One of the earliest indications that abnormal fibroblasts could promote cancer came from the laboratory of Seth and Ana Schor, who showed that fibroblasts from tumours had a fetal phenotype, characterized by the production of migration-stimulatory factor (MSF), which was also expressed by normal-appearing fibroblasts from cancer patients with a familial history of cancer. MSF is a truncated form of the oncofetal isoform of fibronectin, which is proposed to contribute to carcinoma development by altering cellular adhesion early in carcinogenesis. This aberrant stromal phenotype might also contribute to a genetic predisposition to cancer by promoting niche formation.

Fibroblasts are extremely heterogeneous and are also crucial sources of proteolytic enzymes, growth factors and cytokines. Fibroblasts are responsible for the production and deposition of the bulk of the extracellular matrix proteins, such as collagen I and fibronectin, as well as matrix metalloproteinases. Although prominent in all tissues, it is not likely that normal fibroblasts participate in precancer niche formation; rather, a subset of activated myofibroblasts that are αSMA⁺ are strongly implicated. Some myofibroblasts originate from bone-marrow-derived MSCs, which are a self-renewing population of cells that have been shown to regulate cancer stem cells through cytokine networks, whereas other myofibroblasts are derived from tissue MSCs or are reprogrammed cells from local sources. As mentioned above, various studies provide compelling evidence that aberrant fibroblast signalling promotes cancer. A model in which Pten is deleted in stromal fibroblasts is characterized by an expansion of the stroma and the initiation of mammary tumorigenesis.
fibroblast niche-forming potential, investigations led by Leland Chung showed that co-injection of transformed fibroblasts (rat NBF-1 or mouse NIH3T3 cells) induced a normally non-tumorigenic cell line to form tumours. Consistent with niche expansion, Cunha and co-workers demonstrated that fibroblasts derived from prostate tumours stimulated tumour progression of prostate epithelial cells immortalized with the simian virus (SV40) T antigen. Such studies suggest that fibroblasts, rather than being innocent bystanders in the tumorigenic process, can convert from tumour-suppressive to tumour-promoting agents.

Detailed studies of early events in gastric cancer induced by infection with Helicobacter species supports the contention that dynamic interactions mediated by MSCs begin very early in the carcinogenic process. As discussed above, this model leads to chronic inflammation and eventual dysplastic lesions. αSMA+ myofibroblasts, generated from MSCs, contribute to both the stromal and bone marrow niche and MSC self-renewal. During chronic inflammation leading to carcinogenesis, these αSMA+ bone marrow niche cells increase in a TGFβ-dependent manner, possibly facilitating niche construction. The CXCR4–SDF1-dependent recruitment of αSMA+ bone marrow stromal cells to sites of dysplasia, together with Gremlin–1-expressing MSCs, act in concert to expand the cancer niche that promotes and stabilizes tumour progression. Notably, inhibition of TGFβ or CXCR4 prevents niche expansion, and significantly reduces dysplasia. Once the TME is established, a biologically distinct cellular phenotype — cancer-associated fibroblasts (CAFs) — is identifiable and functionally active, and is often derived from different cell types, including MSCs.

The maturing cancer niche

In order for cancer to evolve from carcinoma in situ into invasive cancer, further changes in both the initiated cell and the niche are required. In this third stage of niche development, selection forces at work on the tumour would seem to favour interactions between cancer cells and stromal cells that increase the availability or variety of growth-inducing signals or immune-suppressive signals.

Changes in bone marrow, such as cell activation and mobilization, in response to tumour development are likely to be integral in niche maturation. The nature of these systemic signals is not fully defined, but could involve TGFβ, SDF1, and possibly exosomes. TGFβ seems to have a major role in the conversion of MSCs into CAFs, and treatment with a TGFβ inhibitor blocks the expansion of CAFs at the tumour site. In addition, TGFβ induces the production of CAFs through an SDF1–CXCR4 axis, and SDF1 is essential for the recruitment of MSCs and CAFs to the tumour site. Overexpression of SDF1 leads to a greater recruitment of MSCs and CAFs, whereas SDF1 antagonism blocks the production of CAFs in the bone marrow, as well as the recruitment of CAFs to the tumour site.

Recent reports suggest that circulating exosomes produced by established primary tumours have an effect on bone marrow progenitors through the horizontal transfer of molecules, such as proteins and microRNAs. Tumour-derived exosomes alter bone marrow progenitors and recruit BMDCs through the upregulation of pro-inflammatory molecules at premetastatic sites. As noted above, tumour cell exosomes also activate CAFs in the local stroma, recruit MSCs and alter T cell function.

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Oncogenic changes in tumour cells can moderate angiogenesis and so influence the maturation of the cancer niche into the TME. For example, sustained activity of the transcription factor MYC in the presence of the anti-apoptotic protein BCL-X, in the islets of the mouse pancreas drives the proliferation of β-islet cells, but also indirectly increases the proliferation of endothelial cells. The cytokine IL-1β produced by the proliferating β-islet cells was shown to be necessary and sufficient for the angiogenic effects of MYC activity. IL-1β expression mediated the activation and redistribution of the angiogenic factor vascular endothelial growth factor A (VEGFA) from the extracellular matrix. Thus, the production of IL-1β induced by MYC in the proliferating β-islet cells serves as a paracrine trigger to modify the microenvironment. Inhibition of IL-1β delayed tumour growth, thus indicating the importance of the effects on the TME.

In a model of breast cancer, enhanced infiltration of macrophages and other myeloid cells was found to always precede the angiogenic switch, which is necessary for the transition between dysplastic and early carcinoma stages. Genetic depletion of myeloid cells by homozygous deletion of the macrophage growth factor, colony-stimulating factor 1 (CSF1), delays both the angiogenic switch and malignant progression of mammary cells expressing the polyoma middle T oncprotein, suggesting that myeloid cells regulate angiogenesis. Overexpression of CSF1 from the mouse mammary tumour virus promoter resulted in an especially early recruitment of macrophages and other leukocytes to hyperplastic lesions in the mammary gland and the extensive development of blood vessels. Thus, premature myeloid cell recruitment was sufficient to stimulate a degree of angiogenesis that is more common in late-stage carcinomas, thus indicating that angiogenic activity is not necessarily a response to enhanced tumour size (and hypoxia), but is controlled by cells that are recruited to the TME, independently of tumour stage.

Just as the ability of a tumour to generate premetastatic niches is likely to be a major factor that determines metastatic spread (reviewed in REF. 87), we speculate that niche-forming interactions affect which transformed cells survive, expand and progress to clinical disease, and thus determine cancer incidence. The multiple cellular candidates that might establish a cancer niche early in carcinogenesis all serve the same purpose: to provide a suitable environment for survival of the cancer cells. Resident, circulating and bone-marrow-derived stromal cells stabilize initiated clones, which secrete factors and exosomes that refine tumour-associated stromal cell phenotypes, elicit angiogenesis and evade immune surveillance. The initial stromal cell interactions with the transformed clone may be adventitious, and thus rate limiting, but at some point, a successful niche evolves and matures into a dynamic feedback system (FIG. 2).

Eliminating the cancer niche

Considering the new insights into the interplay between cancer cells and stromal cells, one might recall Stephen Paget’s theory of “seed and soil” in metastatic disease. Indeed, recent studies suggest that the early use of systemic therapies targeted to the metastatic microenvironment may be beneficial, perhaps even as an adjunct to the initial treatment of the primary tumour (reviewed in REF. 87). Yet, the ‘soil’ is prepared long before metastatic growth. We suggest that greater attention should be paid to the niche when designing therapies to prevent and treat cancer. If cancer is initiated in part by carcinogenic effects on the stroma, as suggested by the responses of experimental models
to radiation and chemical carcinogens, then chemopreventive agents aimed at the stroma to avert niche expansion would be a reasonable strategy to reduce risk or inhibit cancer progression to clinical disease. Anti-inflammatory agents, particularly those directed to chronic ‘smouldering’ inflammation (as opposed to acute inflammation) might be effective. Alternatively, activated phenotypes in macrophages and fibroblasts might be suppressed by inactivating or dampening epigenetic switches, as has been experimentally achieved using differentiating agents such as 5-azacytidine.

As niches are by nature highly localized, and incipient cancer is undetected, ideas for targeting the precancer niche may be inferred from the factors that augment carcinogen efficiency or from studying tissue samples from individuals who have a high risk of developing cancer. Of special interest is age- ing: could the higher risk of cancer in older individuals be reduced by eliminating the potentially ‘permissive’ microenvironment? The observation that only 4% of people aged over 100 years die of cancer in comparison to 40% of those aged 50–69 (REF. 26), indicates that this is physiologically achievable and might be emulated pharmacologically if it was better understood. Those who live to be quite old seem to have an immune system that efficiently resolves acute inflammation and suppresses chronic inflammation. This duality is evident in the chemical carcinogenesis model of skin cancer, in which the genetic control of a strong acute inflammatory response to TPA is associated with a reduced incidence of skin tumours, whereas a chronic inflammation response is strongly associated with cancer susceptibility 9. Strategies to personalize cancer medicine by using agents that interrupt aberrant signalling in cancer cells are typically short-lived because of resistance. Therapeutic success should include not only the eradication of malignant tissues, but also therapies that may provide long-term control of cancer by reverting a hospitable niche. For example, α-interferon treatment in chronic myeloid leukaemia re-establishes the interaction between haematopoietic progenitor cells and the bone marrow stroma and thereby reduces proliferation 90,91. That some therapeutic agents may already act through effects on the microenvironment provides support for turning attention to even earlier events in the cancer niche.

Conclusions

Recent initiatives to understand the biology of stromal cells that contribute to tumour growth and survival have produced new strategies to control cancer. We think that understanding the carcinogenic process as being a balanced partnership of stromal and cancer cells will not only provide keys to controlling cancer, but will also be crucial for cancer prevention.

Several authors have described cancer in terms of evolution, ecology and emergent properties 92–94, frequently focusing on two important concepts: the impact of selection at different levels of organization and the role of fitness in cancer cell dynamics. However, fitness is only relative to the particular microenvironment of those cells. This implies that there are two sides to the coin of somatic evolution: changes in the neoplastic cells and changes in their environment that alter the selective pressures on the neoplastic cells. Here we propose the concept of a dynamic niche that expands on these concepts. We speculate that niche construction, like initiation, is often stochastic, and thus not subject to evolutionary selection at the level of the organism; however, once a cooperative interaction is established, evolutionary processes would act to select the most productive phenotypes of both malignant and normal cells. In other words, these novel ecological relationships may be due to an unfortunate convergence, but construction of a niche results in successful co-evolution that promotes cancer progression. Indeed, fortuitous interactions between initiated cells and specific stromal cells result in an emergent property in which both stromal and tumour cell participants of a niche are necessary for survival, that is, fitness. A cancer prevention strategy might disable the niche, which has a relatively limited phenotypic repertoire within and between individuals, or re-educate its normal cell constituents. The next stage of carcinogenesis, promotion, parallels niche expansion through tissue remodelling and the recruitment of stromal cells and BMDCs. The maturation of the niche supports progression to clinically evident cancer and produces the TME that actively contributes to invasion and metastasis.

New models and methods are needed to study the dynamic changes in stromal cells that enable initiated cells to survive and
progress, and to test cancer prevention strategies that tip the balance towards tumour suppression. In contrast to the tools that are available for studying an established TME, niche formation results from rare, stochastic cell interactions that create specialized microenvironments for presumably undetectable initiated cells; therefore, defining crucial parameters of niche formation requires different approaches. Tissue studies of rare events using a combination of in situ localization, informative biomarkers and statistical modelling will identify specific patterns. Dynamic modelling using complex in vitro models will be important for demonstrating instructive interactions, identifying crucial pathways and finding control points that are susceptible to therapy. For example, quantitative modelling of the angiogenic switch predicted that a potential growth plateau that results from a dynamic balance between angiogenic stimulation and inhibition is a possible therapeutic target. When the distinctive behaviours of stromal cells under the influence of cancer cells are better understood, we suggest that they can be targeted without harming immune, inflammatory or stromal cells elsewhere in the body. Such strategies may provide the long sought means to control a root cause of cancer: the corruption of local and systemic environments.

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factors that regulate tumor growth and development. An understanding of the molecular mechanisms by which tumor stromal cells influence tumor behavior is critical for the development of new anti-cancer therapies.

**FURTHER INFORMATION**

Mary Helen Barcellos-Hoff's homepage: http://www.med.nyu.edu/biosketch/barcemonyl.html

David Lyden's homepage: http://www.med.nyu.edu/research/idc/dept/index.html


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