The stem-cell niche as an entity of action

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Stem-cell populations are established in 'niches' — specific anatomic locations that regulate how they participate in tissue generation, maintenance and repair. The niche saves stem cells from depletion, while protecting the host from over-exuberant stem-cell proliferation. It constitutes a basic unit of tissue physiology, integrating signals that mediate the balanced response of stem cells to the needs of organisms. Yet the niche may also induce pathologies by imposing aberrant function on stem cells or other targets. The interplay between stem cells and their niche creates the dynamic system necessary for sustaining tissues, and for the ultimate design of stem-cell therapeutics.

In architecture, the word niche refers to a recess, and in ecology it refers to a habitat where an organism can reside and reproduce; in French, it refers to a dog-house. So, the grand position of the stem cell in popular concepts of science is appropriately humbled by the cells dwelling in a place where they might awaken with fleas. However, the niche does provide both conceptual and physical depth to the stem cell. Stem cells are, after all, defined by their function in complex multidimensional environments over time. Stem cells are by themselves of limited interest, but the integration of stem cells and their descendents into tissues is the basis for higher forms of life. Therefore, the niche is as critical as stem-cell-autonomous functions in shaping our understanding of basic stem-cell biology, and how it contributes to health and disease.

Although a place of residence would fulfil the architectural conception of the niche, it is inadequate in regard to stem cells. The niche in cell biology is more appropriately considered along ecologic lines, and requires a sustaining function. The simple location of stem cells is not sufficient to define a niche. The niche must have both anatomic and functional dimensions, specifically enabling stem cells to reproduce or self-renew. This becomes particularly important as new sites of stem-cell localization are defined.

Adult or somatic stem cells generally have limited function without the niche. A case in point is the haematopoietic stem (HS) cell, which regenerates the entire blood and immune system, and makes copies of itself after limit-dilution transplantation. HS cells circulate freely, but seem to have little function outside specific anatomic locations. It is specific cues from specific sites that allow stem cells to persist, and to change in number and fate. Importantly, it is also the niche that provides the modulation in stem-cell function needed under conditions of physiologic challenge. It is this dynamic capability that makes the 'niche' concept particularly important and central to the realization of regenerative medicine. It is the ability of the niche to impose functions on stem cells that makes the concept important in disease. We are now at a time when descriptive studies are giving way to those of physiology. This review attempts to integrate the issues of niche components, signals and modification, and determinism imposed by the niche to portray the dynamism inherent in niche biology.

Niche elements reconsidered: the role of extracellular matrix

The concept of a niche as a specialized microenvironment housing stem cells was first proposed by Schofield almost 30 years ago in reference to mammalian haematology[1], although experimental evidence was first provided by invertebrate models. In the gonads of *Drosophila melanogaster* and *Caenorhabditis elegans*, the germ stem cells reside at the distal end of a tapered structure, and have been shown to depend upon interactions with somatic cells at the end of that structure to maintain stem-cell features[2–4]. The notion that heterologous cell types compose the niche was well supported by this early work and has led to emphasis on defining similar cell-based niche components in mammalian tissues. This has yielded identification of the osteoblast in the bone marrow, and the endothelium in the brain, and possibly in the bone marrow[5–8]. Whether there is a necessity for another cell type — other than the stem cell — to be present for a niche to function, however, has recently been brought into question.

Two reports have demonstrated that the posterior mid-gut populations of cells in *Drosophila* have the capacity to produce daughter cells of at least two types: enterocytes and enteroendocrine cells[9,10]. These cells seem to be able to self-renew and provide a long-lived ability to generate more mature offspring in a clonal manner. Notably, however, these cells do not appear to be in direct contact with a heterologous cell type. They do have focal localization of the β-catenin paralogue, Armadillo, at the interface between the stem cell and its descendant daughter cell (the enteroblast), but this is distinct from the cells of different lineages composing most previously defined niches. The stem cells in this case sit on a basement membrane that divides them from surrounding muscle cells. It is suggested that the basement membrane itself might participate in the specialized microenvironment, possibly providing an opportunity for shifting location of the stem cell, sliding along a continuum of the intestine. These data challenge the expectation that heterologous cells must necessarily be within the niche, and suggest that some stem cells might have a niche composed of extracellular matrix and other non-cellular constituents that could regulate their control (Fig. 1).

The concept of extracellular matrix regulating primitive cells is long-standing and at least three examples now exist in mammalian stem-cell systems. The first is in the skin, where β-1 integrins are known to be differentially expressed on primitive cells and to participate in constrained localization of a stem-cell population through presumed interaction with matrix glycoprotein ligands[11,12]. Second, in the nervous system, absence of tenascin C alters neural stem-cell number and function in the subventricular zone[13]. Tenascin C seems to modulate stem-cell sensitivity to fibroblast growth factor 2 (FGF2) and bone morphogenetic protein 4 (BMP4), resulting in increased stem-cell propensity to generate glial offspring. In the haematopoietic system, tenascin C deletion has also been shown to affect primitive cell populations, raising the possibility that it participates in several stem-cell niches[14].

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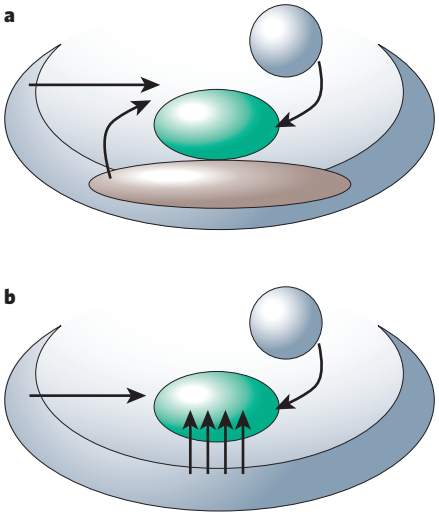

Figure 1 | Refining elements necessary for an adult stem-cell niche. a, Early studies provided evidence that heterologous cell types created a three-dimensional structure in which stem cells reside. **b,** Recent data raises the possibility that a regulatory microenvironment might include stem cells simply resident on the basement membrane with homologous cell–cell interactions. Stem cells are shown in deep green and more mature offspring are represented by a lighter shade.

Third, another matrix protein, the Arg–Gly–Asp (RGD)-containing sialoprotein, osteopontin (OPN), has now been demonstrated to contribute to HS-cell regulation[15,16]. Implicated previously in tumour metastasis and cell-mediated immunity[17,18], OPN interacts with several receptors known to be on HS cells, CD44, and α4 and α5β1 integrins[19,20]. It is produced by multiple cell types, among them osteoblasts that contribute to the HS-cell niche. Notably, OPN production can vary markedly, particularly with osteoblast activation. Animals deficient in OPN have an increased HS-cell number, owing to a mechanism that is still debated but is microenvironment dependent[15,16]. Without OPN, superphysiologic stem-cell expansion occurred under stimulatory conditions[15]. Therefore, OPN seems to serve as a constraint on HS-cell number, limiting the number of stem cells under homeostatic conditions or with stimulation. Taking these three scenarios together, matrix components provide localizing niche elements that can contribute stimulatory, or impose inhibitory, influences on the stem-cell pool. They, like other stimuli in the niche, balance opposing possibilities.

Paracrine factors and niche structure

Cells and extracellular-matrix components in the stem-cell niche are relatively predictable, although the complexity and integration of these elements is far from understood. Soluble mediators of cellular response would also be expected and a number have been defined that are important paracrine regulators of stem-cell function. Within the *Drosophila* testis, Unpaired (UPD) is secreted by niche (hub) cells and induces stem-cell self-renewal via Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signalling[21,22]. In the *Drosophila* ovary, Decapentaplegic (DPP) is secreted after proteolytic cleavage and, along with another BMP analogue, Glass bottom boat (GBB), is produced by niche (cap) cells[23,24]. These stimulate SMAD signalling in the germ stem cells and result in suppression of differentiation, maintaining the self-renewing stem-cell state[25]. Wingless-related proteins (WNTs) and their antagonists, soluble Notch modulators, FGFs and Hedgehog (HH) also contribute input in a paracrine manner with varying capacity to induce proliferation or impair differentiation. HH, however, has an additional intriguing function: it is secreted by cap cells and mediates proliferative effects not just on germ stem cells, but also on surrounding somatic cells composing the niche itself in the *Drosophila* ovary[26,27]. This effect on niche composition is a common theme of HH extending to mammals.

HH family members have a role in topographic organization and formation of niches in development. Sonic hedgehog (SHH) is essential for hair-follicle formation, and distinguishes the localization of specific subsets of epidermal stem cells to either the follicular niche or the interfollicular epidermis[28,29]. In addition, SHH participates in specific spatially restricted events within established niches. Hair represents a uniquely dynamic physical association of elements within a niche, owing to the change in distance during the hair cycle of the dermal papilla from the bulge region where at least some stem cells reside. Expression of SHH is spatially and temporally restricted, and seems to modulate new hair formation[30], which is a function amenable to small-molecule manipulation[31]. In the developing intestine, SHH and Indian hedgehog contribute to architectural patterning, playing a key part in assembly, dimensions and regularity of the crypts where stem cells reside[32]. Therefore, HH contributions to stem-cell control are morphogenic, creating a niche, and regulating stem-cell fate within that niche.

Maintaining physical organization of the established niche is probably an active and important process; however, the signals governing it are not well defined. Indirect evidence suggests that ephrins, important mediators of structural boundaries in neural and vascular tissue, might participate in at least one stem-cell system. Graduated expression of ephrin B1 and, reciprocally, its transmembrane tyrosine kinase receptors, EphB2 and EphB3, has been elegantly shown to organize mouse intestinal epithelial cells[33]. Disrupted expression of the receptors leads to aberrant organization of crypt and villus cells, including cells at the interposition between them, which are defined as stem cells. The altered topographic orientation of primitive and maturing cells results in polyploid outgrowths. Therefore, it will be important to discern molecular events sustaining architectural organization of the niche, particularly in considering how niche elements might participate in dysregulated growth in tumours.

Metabolism as an underexplored variable

Cells, matrix glycoproteins and the three-dimensional spaces they form provide ultrastructure for a stem-cell niche. The contact between these elements allows molecular interactions that are critical for regulating stem-cell function. Secreted proteins offer a paracrine measure of control, but non-protein components of the local microenvironment also affect stem-cell function. One such participant was examined for the haematopoietic niche based on the unusual mineral composition of the bone adjacent to which at least a portion of the stem cells reside. It was proposed that because the endosteal surface is the location of bone remodelling, and osteoblasts and osteoclasts are often co-localized, the known high ionic calcium concentrations that exist near active osteoclasts might influence stem-cell function. Osteoblasts express receptor-activator of nuclear factor-B ligand (RANKL), which is essential for osteoclast differentiation and, thus, the proximity of osteoblasts and osteoclasts. At the site of active bone remodelling, ionic concentrations have been observed that dramatically exceed serum levels and vary with osteoclast activity. Cells sense extracellular ionic calcium through the seven membrane-spanning calcium-sensing receptor (CaR). This G-protein-coupled receptor was found to be expressed on a stem-cell-enriched population of bone-marrow haematopoietic cells, as well as select subsets of mature haematopoietic cells[34]. Stem cells from mice genetically engineered to be CaR deficient had a markedly abnormal ability to engraft the bone marrow. They were functionally normal in the fetal liver and spleen, but were unable to engage with or be retained at the endosteal niche. Simple molecules, including inorganic ions, might contribute to niche function.

Metabolic products, such as calcium, which influence stem-cell behaviour in the niche are likely to represent a dimension of stem-cell control that allows cells to respond to varying conditions of tissue state. For example, oxidative stress markedly affects stem-cell function. Under conditions in which 'ataxia telangiectasia mutated' (ATM) deficiency was induced, reactive oxygen species (ROS) accumulated in HS cells in the bone marrow[35]. This was associated with increased

levels of the cyclin-dependent kinase inhibitor associated with senescence, p16INK4a, and with evidence of markedly decreased stem-cell function. Modifying ROS with anti-oxidants reduced p16INK4a and rescued stem-cell function. Challenges of oxidative stress are therefore likely to be important in altering stem-cell fate. The changing local metabolic conditions reflecting tissue state might thereby provide real-time information to modulate stem-cell function. Metabolic sensing is a likely mechanism by which stem cells gauge the 'needs' of a tissue or organism (Fig. 2). This requires further detailed anaylsis.

What changes in a niche?

Experimental examination of systemic inputs to the niche might include measuring stem-cell number or proliferation. However, the haematopoietic system provides an additional feature, stem-cell trafficking, which can be readily quantitated, making it attractive as an experimental model. Stem-cell entry and exit from the niche are important components of haematopoietic niche function that are essential in development and persist in the adult.

Blood formation in early development occurs in distinct extra-embryonic and embryonic sites. The yolk sac, aorto-gonadomesonephros (AGM), placenta and fetal liver participate in embryonic and definitive haematopoiesis in temporal sequence. Early haematopoietic-cell production occurs with apparent independence in the yolk sac and AGM regions. When the fetal liver becomes a source of blood-cell production, this is thought to occur by virtue of cells migrating from the AGM or placenta. Similarly, as haematopoiesis transitions to the bone marrow, migration rather than *de novo* generation is thought to be critical. This is best exemplified by mice made genetically deficient in CaR, or in the chemokine CXCL12 or its cognate receptor CXCR4, which have normal production of fetal liver HS cells, but fail to transition to haematopoiesis in the marrow space[34,36,37]. These phenotypes are due to HS cells failing to move to the marrow niche.

The migratory nature of HS cells is therefore fundamental to their developmental programme and remains ongoing in adulthood. HS cells are found in the blood even under homeostatic conditions in mice and, from what can be estimated on the basis of imperfect measures, also in humans. These numbers can be dramatically modified on the basis of stimulation by several cytokines, including granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage (GM)-CSF and interleukin-8 (IL-8). The kinetics of mobilization by these factors varies markedly, reflecting differing mechanisms; however, one mechanism not appreciated until recently is the ability of G-CSF to modify niche cells. G-CSF is capable of altering osteoblast activity sufficiently to reduce production of CXCL12, despite the absence of G-CSF receptors on these cells[38]. It was an elegant, if serendipitous, discovery that mice with altered sympathetic nervous system function lack the ability to mobilize stem cells from the bone marrow in response to G-CSF[39]. Sympathetic nervous system input, whether induced by G-CSF or by neural agonists, modulates the niche sufficiently to change the localization of stem cells. As the nervous system is inherently a circuit capable of connecting anatomically disparate tissues, these studies indicate one potential means by which the stem cell might be able to 'sense' changes in the state of the tissue or the organism. If there are changes, such as distant injury, neural connections might mediate the response even at the stem-cell level.

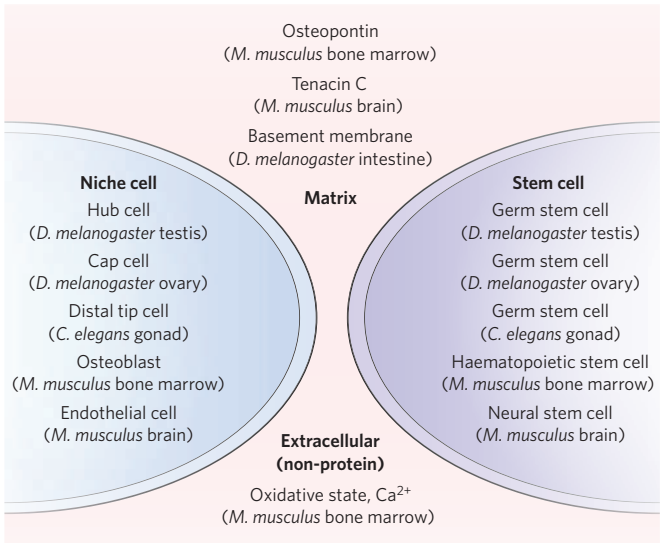

Figure 2 | Elements identified in stem-cell niches from various organisms and tissues. Intentionally excluded are the complex molecular interactions that are present at the interface between the stem cell and its niche cell counterpart. These are reviewed extensively elsewhere[54,55]. *C. elegans*, *Caenorhabditis elegans*; *D. melanogaster*, *Drosophila melanogaster*; *M. musculus*, *Mus musculus*.

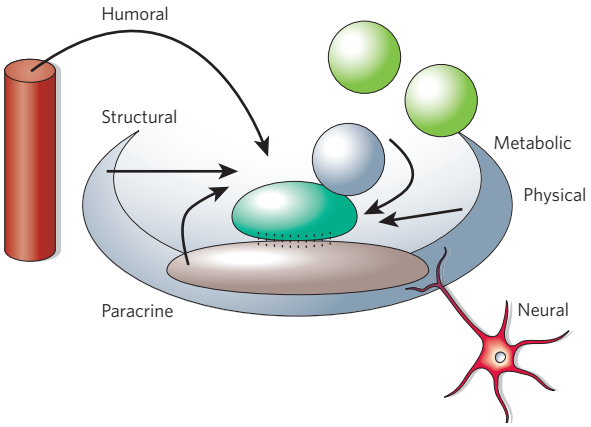

Figure 3 | Inputs feeding back on stem-cell function in the niche. Elements of the local environment that participate in regulating the system of a stem cell in its tissue state are depicted. These include the constraints of the architectural space, physical engagement of the cell membrane with tethering molecules on neighbouring cells or surfaces, signalling interactions at the interface of stem cells and niche or descendent cells, paracrine and endocrine signals from local or distant sources, neural input and metabolic products of tissue activity.

Besides the nervous system, an obvious ready means of connecting localized sites with information from a distance is the circulatory system (Fig. 3). HS cells might directly exploit their frequent blood trafficking to 'survey' input at a distance and some other stem-cell types might do the same[40–42]. More likely is the physical association of stem cells with the microvasculature. In development, the co-localization of endothelial cells and progenitor populations from tissues as diverse as pancreas, heart, brain, liver, adrenal, bone and blood reflect the potential for regulatory signals generated by endothelium or nascent vasculature to affect primitive cell fate (reviewed in ref. 43). The adult hippocampus continues to generate neurons from precursor populations in perivascular loci that contain proliferating neural precursors, angioblasts and glial cells[7]. This region has been called an 'angiogenic niche'. Similarly, HS cells have been observed in abundance in close physical association with bone-marrow microvessels using recently defined immunohistochemical reagents[8]. The sites on such vessels where primitive cells engage and diapedese seem to be highly discontinuous, and are functionally distinguished by abundant CXCL12 and E-selectin expression[44]. Although cells seem to reside there, only indirect data suggest that this represents a location that is regulating stem-cell function rather than just serving as a way-station for highly mobile cells. It is likely that the perivascular site is indeed a niche; however, at present, the data on function that are necessary to confirm this conclusion are lacking for stem cells. The haematopoietic cells known to be regulated in association with marrow vessels are committed progenitors[45].

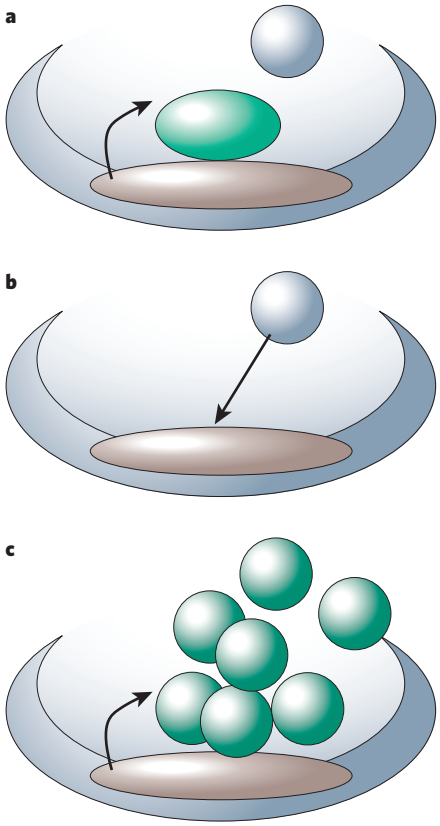

Figure 4 | Potential niche contribution to dysplastic cell growth. a, Normal interactions and occupancy of the niche tightly controls stem-cell number. **b,** Vacancy in the niche might result in ectopic occupancy by another cell type. **c,** Niche signals might impose proliferative or de-differentiative signals, contributing to a disordered state of tissue organization and control.

Although association with microvessels is an intuitively compelling means for a stem cell to be in an environment where system-wide signals can be sampled, the exact components of the vasculature that engage stem cells are still unclear. In certain circumstances, such as islet-cell proliferation, the basement membrane may again provide regulatory information[46]. Endothelial cells have been implicated as directly inducing neural precursor Notch activation with resultant cell proliferation and differentiation in a manner that vascular smooth muscle cells do not[47]. Pericytes surrounding the endothelium might contribute to stem-cell regulation, and have been found to be closely associated with mesenchymal stem cells[48]. Endothelium, pericytes and surrounding smooth muscle are all candidate contributors to a perivascular niche for normal stem cells. They might also contribute to the foci of tumour-initiating or cancer stem cells thought to be responsible for blood-borne metastases. Recently, it was shown that such a site could be rendered more conducive to cancer-cell engraftment if modified by intravascular delivery of bone-marrow-derived vascular endothelial growth factor receptor 2 (VEGFR2)-positive cells[49]. The idea that stem-cell niches can be modified or created has experimental support in other systems as well.

Under conditions of stress, such as fibrosis of the bone-marrow space, extramedullary haematopoiesis develops in humans and mice. Sites such as the spleen might re-kindle a developmental vestige (particularly in the mouse, in which the spleen is a haematopoietic organ) or engage entirely new sites, such as lymph nodes or soft tissue. These seem to function as regulatory niches for stem cells. Experimentally, niches can be generated by altered expression of single genes. Stabilized β-catenin expressed under the control of an epidermal-specific promoter resulted in *de novo* generation of hair follicles with a presumed attendant stem-cell pool[50]. Therefore, niches are not static in function or number, and can be created or made to change under specific conditions.

What can a niche change?

The variability in niche number and function implicitly raises the issue of whether such modifications can participate in disease states or be induced to achieve therapeutic outcomes. Although altering normal stem-cell function is clearly one potential effect of altered niche dynamics, another more ominous possibility has been raised by lessons learned in *Drosophila*. Experimentally-induced stem-cell vacancy in the ovarian germ stem-cell niche did not result in immediate loss of niche structural integrity or potential. Rather, the empty niche could be occupied by somatic cells and, if not terminally differentiated, ectopic proliferation could ensue[51]. Furthermore, altered expression of a niche product, such as DPP, could induce more mature progenitor populations (cystocytes in *Drosophila*) to revert to a stem-cell phenotype[52]. A stem-cell state could be imposed upon more mature cells. Although neither of these scenarios has been explored in vertebrate systems, these mechanisms could be predicted to result in niche-generated disease. Indeed, altering cells to acquire more stem-like features is consistent with recent applications of stem-cell biology to the understanding of cancer. The stem-cell paradigm might be more than just a means of understanding how malignant tissue is organized and how cancer might be modified by a specific microenvironment. It raises the real possibility that a dysfunctional microenvironmental niche might contribute to the emergence of the disease (Fig. 4).

Modifying the niche

If the niche is a dynamic structure that has the capacity to be formed anew, to respond to exogenous signals and to include varying components, this raises the question of whether the niche can be a target for therapeutic manipulation. There are compounds defined for use in other settings that could be considered for 're-purposing' to affect the niche. Certainly, within the haematopoietic system, the association of the stem cell with bone raises the possibility that compounds developed for the modification of bone or mineral metabolism might have a role. Candidates include drugs that affect the osteoblast or osteoclast function of inhibiting molecular regulators of stem-cell interactions with the niche, such as drugs targeting the CaR and OPN receptors, or Notch. Experimental evidence has shown that altering the niche pharmacologically can change stem-cell outcomes, with physiologic impact. For example, the use of parathyroid hormone (PTH) to stimulate the receptor on osteoblasts resulted in an increase in the number of stem cells under homeostatic conditions. When the setting was the physiologic stress of bone-marrow transplantation, dramatic results were noted. The animals receiving PTH had markedly improved marrow cellularity and increased rates of survival[5]. The stem cells do not have PTH receptors, so the effects are indirect and probably mediated by niche osteoblasts. This effect has been shown to protect resident HS cells from cytotoxic damage during exposure to chemotherapy drugs, to improve harvests of stem cells from treated animals and to improve engraftment outcome. Whether this paradigm of identifying characteristics of a niche to permit rational pharmacologic manipulation can be applied to other stem-cell systems needs to be tested further. However, if demonstrated, this would offer a novel approach to regenerative medicine.

The niche as a target in cancer therapy

With the recent development of the cancer stem-cell concept, which was first proposed half a century ago but was only empirically shown by the pioneering work of Dick and others, another dimension of the niche as a 'druggable' target is beginning to take shape[53]. If cancer is organized in a manner similar to normal tissue, with a minor subpopulation of stem cells, an attendant blood supply and a unique microenvironment, there might be a similar dependence of the stem cells on a cancer niche. The possibility of a niche has been shown by multiple studies indicating distinctive features of non-cancerous cells within a tumour, and by the recent report of a population of bone-marrow-derived cells paving the way for subsequent establishment of

a tumour focus. If the components of this niche could be demonstrated and targeted, it would be of considerable interest to modify the relative support of the stem-like cells of cancer. The idea that the niche might be a druggable target would be extremely appealing as an adjunctive and entirely independent means of targeting malignant cells. Perhaps the niche will be more than a biologist's puzzle, and will become a guide for novel therapies to enhance the regenerative capacity of normal stem cells and limit the malignant potential of cancerous ones. ■

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