STEM CELLS

No place like home: anatomy and function of the stem cell niche

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Abstract | Stem cells are rare cells that are uniquely capable of both reproducing themselves (self-renewing) and generating the differentiated cell types that are needed to carry out specialized functions in the body. Stem cell behaviour, in particular the balance between self-renewal and differentiation, is ultimately controlled by the integration of intrinsic factors with extrinsic cues supplied by the surrounding microenvironment, known as the stem cell niche. The identification and characterization of niches within tissues has revealed an intriguing conservation of many components, although the mechanisms that regulate how niches are established, maintained and modified to support specific tissue stem cell functions are just beginning to be uncovered.

Niche
An anatomical structure, including cellular and acellular components, that integrates local and systemic factors to regulate stem cell proliferation, differentiation, survival and localization.

Stromal cell
A type of cell that contributes to the structure and connective tissue aspects of an organ.

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Stem cells are responsible for the growth, homeostasis and repair of many tissues. The maintenance and survival of stem cells is regulated by inputs from their local microenvironment, often referred to as the 'stem cell niche'. The stem cell niche hypothesis was developed in 1978 by Schofield, who proposed that stem cells reside within fixed compartments, or niches, which are conducive to the maintenance of definitive stem cell properties[1]. Thus, the niche represents a defined anatomical compartment that provides signals to stem cells in the form of secreted and cell surface molecules to control the rate of stem cell proliferation, determine the fate of stem cell daughters, and protect stem cells from exhaustion or death.

Elegant experiments in model organisms such as worms and flies provided the first visualization of stem cell niches *in vivo*, and subsequent genetic experiments have confirmed the importance of the niche in regulating stem cell behaviour[2–9]. Recently, new tools for labelling stem cells *in situ* have also facilitated the localization and characterization of stem cell niches in mammalian tissues[10–15]. In addition to providing concrete evidence that niches are essential for proper stem cell function, these studies have revealed that stem cell niches are as varied as the stem cells they support. Moreover, recent work indicates the existence of distinct functional classes of niche, each specialized to sustain the unique functions of particular tissues. Finally, increasing evidence implicates deregulation of the stem cell niche as a proximal cause of many pathologies associated with tissue degeneration[16], ageing[17–20] and tumorigenesis[21–24].

As discussed below, studies in model organisms such as *Drosophila melanogaster* and *Caenorhabditis elegans* have revealed several features of stem cell niches that are important for controlling stem cell behaviour. First, signals that emanate from the niche regulate stem cell self-renewal, survival and maintenance[2–3,5–7]. Second, the particular spatial relationship between stem cells and support cells can polarize stem cells within the niche to promote asymmetric stem cell divisions[25,26]. Third, adhesion between stem cells and supporting stromal cells and/or the extracellular matrix (ECM) anchors stem cells within the niche in close proximity to self-renewal and survival signals[27,28]. Because recent developments have facilitated the localization and visualization of stem cells within mammalian tissues *in vivo*, it is becoming clear that these key features of stem cell niches are also used in more complex stem cell systems. Thus, the stem cell niche provides structural support, trophic support, topographical information and the appropriate physiological cues to regulate stem cell function in both invertebrate and vertebrate organisms (FIG. 1).

In this review, we discuss current concepts and questions surrounding stem cell niches and their role in regulating tissue maintenance and repair. Stem cells hold tremendous potential to reveal fundamental mechanisms of cell fate specification and tissue growth, as well as to stimulate novel approaches for tissue repair and replacement. Yet one of the largest hurdles to the better understanding of these cells and their use in regenerative medicine is the establishment of *ex vivo* systems that support normal stem cell function — including self-renewal and appropriate lineage-specific differentiation.

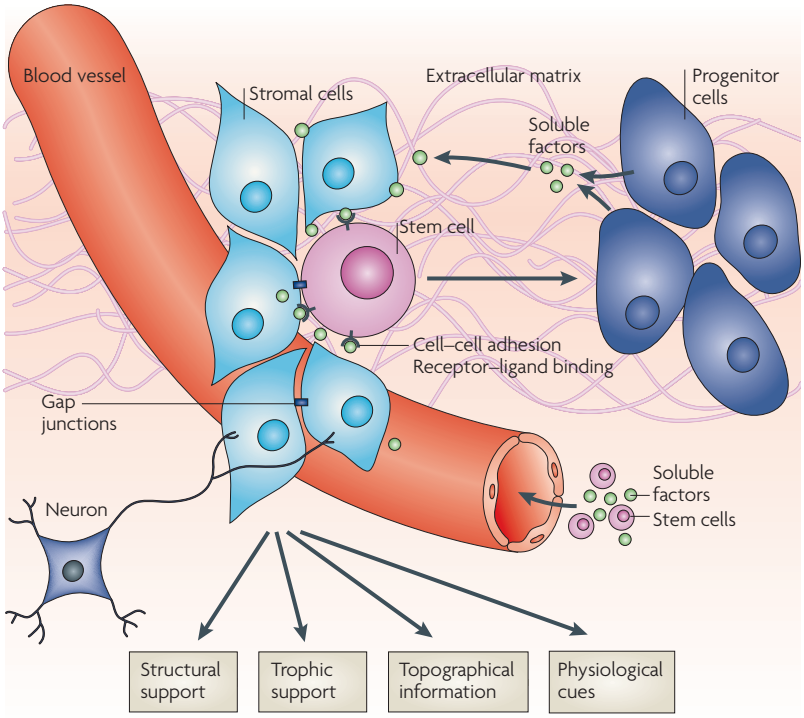

Figure 1 | **Components and functions of stem cell niches.** The niche is a complex and dynamic structure that transmits and receives signals through cellular and acellular mediators. This schematic depicts a hypothetical niche composite, which summarizes known components of previously described mammalian and non-mammalian niches: the stem cell itself, stromal cells, soluble factors, extracellular matrix, neural inputs, vascular network and cell adhesion components. It is important to note that although many niche components are conserved, it is unlikely that every niche necessarily includes all of the components listed. Instead, niches are likely to incorporate a selection of these possible avenues for communication, specifically adapted to the particular functions of that niche, which might be to provide structural support, trophic support, topographical information and/or physiological cues.

Only by uncovering the intimate relationship between stem cells and their surroundings can we hope to achieve the necessary insights that will enable the development and use of such systems.

Stem cell niches

To understand how the local microenvironment can protect stem cells and influence their behaviour, it is first necessary to determine where stem cells reside. Identifying and characterizing stem cell niches has been complicated by the fact that stem cells are extremely rare and, in many cases, specific markers allowing the definitive identification of stem cells *in vivo* are lacking. Nonetheless, much progress has recently been made in identifying stem cell niches, especially within mammalian tissues. For example, many haematopoietic stem cells (HSCs) reside along the endosteal surface of trabecular bone in close proximity to both bone-forming osteoblasts and the endothelial cells that line blood vessels[13,15,29]. HSCs can leave this niche, enter the circulation and return to the niche, and their proximity to endothelial cells may facilitate mobilization from the bone marrow into the circulation[30]. Neural stem cells (NSCs) can be found in two different locations in the brain: within the subventricular zone of the hippocampus and in the olfactory bulb. In both niches, NSCs are located adjacent to endothelial cells, similar to HSCs[10,11]. Such close association of stem cells with the tissue vasculature could be important to expose these cells to systemic factors that may promote their survival, regulate self-renewal and differentiation potential, and/or communicate 'damage' signals to activate their proliferation.

Epithelial stem cells reside within a specialized region of the outer root sheath of the hair follicle, known as the follicular bulge. These multipotent stem cells can contribute to the regeneration of the hair follicle and sebaceous glands, as well as the interfollicular epidermis[14], although they do not appear to be necessary for normal, homeostatic replacement of epidermal cells[31–33]. Stem cells that repopulate the interfollicular epidermis, known as basal keratinocytes, are found at the base of the epidermis, immediately above a basement membrane that separates them from the underlying dermis[34]. Within the mammalian small intestine, gut stem cells reside at the base of intestinal crypts and divide to produce daughter cells that differentiate as they migrate upwards towards villi that extend into the intestinal lumen[35]. Although intestinal stem cells (ISCs) were initially thought to reside immediately above Paneth cells in the crypts (at position +4)[36], recent lineage tracing analysis has instead revealed that their activity tracks to a novel population of crypt base columnar cells (CBCs) that are marked by the expression of LGR5 (Leu-rich-repeat-containing G-protein-coupled receptor-5) and are interdigitated between Paneth cells[37]. Spermatogonial stem cells (SSCs) maintain spermatogenesis throughout the lifetime of adult males. SSCs are located adjacent to the basement membrane along the periphery of the seminiferous tubules of the testis[38]. Recent studies have demonstrated, however, that the distribution of undifferentiated spermatogonia, which probably includes SSCs, is not random. These cells appear to preferentially localize close to the vascular network and interstitial cells that exist between adjacent tubules[39]. Skeletal muscle stem cells, a subset of muscle-fibre-associated satellite cells, are found along the length of the myofibre, in close contact with the myofibre plasma membrane and beneath its basement membrane[40–42]. Interestingly, it appears that tissue stem cells often reside in locations where they are relatively protected from damage (such as environmental toxins[35] or ultraviolet irradiation[14]) compared with the more differentiated cells that they produce. Specific features of each of these niches are discussed in more detail below (TABLE 1).

Components of stem cell niches

Prototypical stem cell niches, including those that support blood, germline and epithelial follicular bulge stem cells, have revealed several physical and functional characteristics that appear to be hallmarks of a stem cell niche (FIG. 1). By synthesizing data from numerous systems, we can generate a hypothetical 'parts list' for stem cell niches, including: the stem cell itself; stromal support cells that interact directly with the stem cell and with each other through cell-surface receptors, gap junctions and soluble factors; ECM proteins that provide structure, organization and mechanical signals to the niche; blood vessels

Trabecular bone
A porous, or spongy, type of bone that is filled with red bone marrow, which appears to be enriched for HSCs in adults.

Osteoblast
A cell that is responsible for bone formation and maintenance.

Seminiferous tubule
The site of spermatogenesis in the testis. The tubules are lined with spermatogonial stem cells and spermatogonia that will eventually progress through meiosis and differentiate into mature spermatozoa. Somatic Sertoli cells also line the tubules and support spermatogenesis by promoting germ cell proliferation and survival.

Table 1 | **Examples of tissue stem cells and their niches**

Tissue	Stem cell	Support cells	Signalling pathways	Adhesion	References
C. elegans gonad	GSC	Distal tip cell*	Notch	NI	2–3, 9
D. melanogaster testis	GSC	Hub cells*	JAK–STAT	DE-cadherin, β-catenin	6, 7, 26, UO
D. melanogaster ovary	GSC	Cap cells* and ESCs	DPP–BMP	DE-cadherin, β-catenin	4, 8, 28
D. melanogaster testis	CPC	Hub cells*	JAK–STAT	DE-cadherin, β-catenin	6, 7, UO
D. melanogaster ovary	ESC	NI	JAK–STAT	NI	117
D. melanogaster ovary	FSC	NI	Hedgehog	DE-cadherin, β-catenin	27
D. melanogaster midgut	ISC	NI	Notch	Possibly to ECM	74–76
Mouse skeletal muscle	Satellite cell	NI	Notch	β1 integrin	65, 118
Mouse bone marrow	HSC	Osteoblasts*, vascular cells	SLF, Wnt, Notch, ANG1, OPN	β1 integrin	13, 15, 29, 46, 64, 110, 119–121
Mouse small intestine	CBC	Crypt fibroblasts, Paneth cells	Wnt, BMP	β-catenin	37, 44, 122, 123
Mouse skin	Interfollicular keratinocyte	NI	Wnt, Shh, Notch	E-cadherin, β-catenin, β1 integrin	124–128
Mouse skin	Follicular bulge stem cell	Dermal fibroblasts	Wnt, BMP	β-catenin, β1 integrin	48, 129, 130
Mouse brain (lateral ventricle)	SVZ stem cell	Vascular cells, astrocytes	Shh, BMP	N-cadherin, β-catenin	10, 131, 132
Rat brain (hippocampus)	SGZ stem cell	Vascular cells, astrocytes	Shh, Wnt	N-cadherin, β-catenin	11, 133, 134
Mouse testis	SSC	Sertoli cells*, vasculature, interstitial cells	GDNF, SLF	α6 integrin, β1 integrin	39, 61, 135–138

ANG1, angiopoietin-1; BMP, bone morphogenetic protein; CBC, crypt base columnar cell; *C. elegans*, *Caenorhabditis elegans*; CPC, cyst progenitor cell (somatic stem cells); DPP, Decapentaplegic; *D. melanogaster*; *Drosophila melanogaster*; ECM, extracellular matrix; ESC, escort stem cell; FSC, follicle stem cell; GDNF, glial cell-line-derived neurotrophic factor; GSC, germline stem cell; HSC, haematopoietic stem cell; ISC, intestinal stem cell; JAK, Janus kinase; NI, none identified; OPN, osteopontin; SGZ, subgranular zone; Shh, sonic hedgehog; SLF, steel factor; SSC, spermatogonial stem cell; STAT, signal transducer and activator of transcription; SVZ, subventricular zone; UO, J. Voog & D.L.J., unpublished observations. *Denotes support cells that have been demonstrated to directly regulate the behaviour of stem cells found within that niche.

that carry systemic signals and provide a conduit for recruitment of inflammatory and other circulating cells into the niche; and neural inputs that might similarly communicate distant physiological cues to the stem cell microenvironment (FIG. 1). Although not all niches necessarily incorporate all of these distinct components, it is clear from this summation that the niche represents a complex and dynamic entity in which the integration of multiple inputs accomplishes exquisite control of stem cell number and function.

Secreted factors. Communication within the niche is essential for the maintenance of proper stem cell function and for determining the rate of stem cell self-renewal. Secreted factors may act locally (within 1–2 cell diameters) or may diffuse throughout the niche to direct stem cell fate decisions. Studies in flies and worms indicated that support cells, which are located adjacent to stem cells, secrete factors that are required for maintaining stem cell identity and for specifying stem cell self-renewal[3,4,6,7,9]. Secreted growth factors have also been shown to regulate stem cell behaviour in mammalian stem cell systems (see below). As our understanding of cellular interactions within the niche remains rather rudimentary, it is likely that future work will reveal tissue-specific stem cell signalling pathways that may be different for each stem cell type and within each stem cell niche.

A survey of the signalling pathways that have been identified in characterized stem cell systems reveals remarkable conservation of the signalling cascades used, but the consequences of activation of these pathways may be different among the various tissues (TABLE 1). One example, which we consider specifically in the following discussion to illustrate this point, is the Wnt signal transduction pathway. Although Wnt signalling has been implicated in many stem cell systems, it appears to be exploited for distinct purposes in each (FIG. 2). In the intestinal epithelium, Wnt signalling appears to be involved in supporting the proliferation of stem cells and transit amplifying cells, as well as directing the differentiation of a specific subset of cells, the Paneth cells, at the base of crypts within the small intestine[43–45]. Although the specific cells that secrete Wnt proteins have not been identified in the intestine, mesenchymal cells surround the crypts and could serve as a local source.

The Wnt signal transduction pathway also has a role in specifying stem cell self-renewal in HSCs. However, rather than being expressed by surrounding stromal cells, Wnt may be secreted from HSCs themselves and might act in an autocrine loop to control stem cell proliferation[46] (FIG. 2). Wnt signalling may be particularly important for mediating the survival of fetal and neonatal HSCs, because experimentally induced deletion of the fetal stem cell marker SOX17 induces expression of the Wnt

Transit amplifying cell
A proliferating cell, derived from tissue stem cells, that lacks long-term self-renewal activity and serves as a precursor for more differentiated cell types.

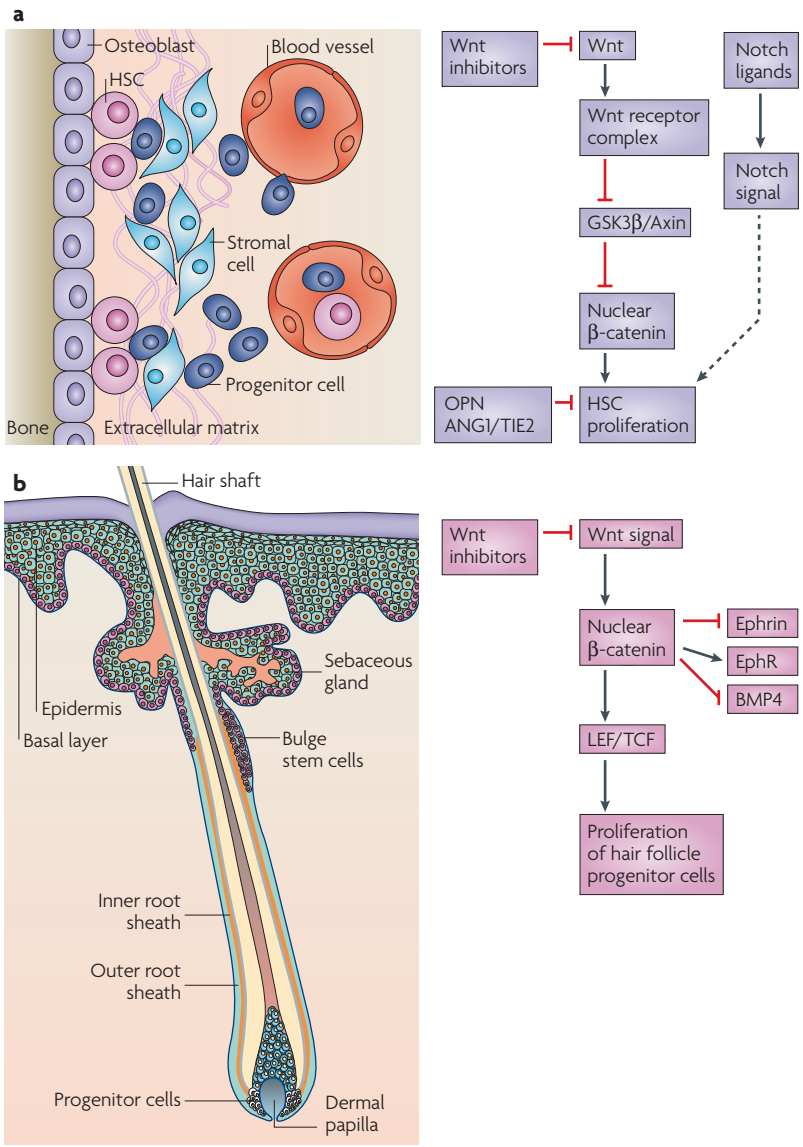

Figure 2 | **Multiple roles for Wnt signalling within stem cell niches.** Wnt signalling can promote cell proliferation, such as self-renewal of haematopoietic stem cells (HSCs) (**a**) or proliferation of transit amplifying cells within intestinal crypts (not shown). Within some tissues, however, Wnt signalling directs the differentiation of specific cell lineages, such as hair follicle precursors (**b**), rather than promoting self-renewal of the multipotent stem cells from the follicular bulge. See the main text and TABLE 1 for more details. ANG1, angiopoietin-1; BMP4, bone morphogenetic protein-4; EphR, ephrin receptor; GSK3β, glycogen synthase kinase-3β; LEF, lymphoid enhancer factor; OPN, osteopontin; TCF, T-cell factor; TIE2, angiopoietin-1 receptor.

antagonist Dickkopf-1 (DKK1) by HSCs and subsequently causes HSC death[47]. It is interesting to consider that the production of growth inhibitory factors by the stem cells themselves could provide a simple mechanism to determine the number of stem cells within a given niche or tissue. The more stem cells that are present, the higher the concentration of growth inhibitory factors, until a threshold is reached that causes an arrest or delay in stem cell proliferation. Conversely, as the stem cell niche becomes depleted of endogenous stem cells, the concentration of inhibitory factors would drop, leading to the activation of stem cell proliferation (or attraction of migrating stem cells) to repopulate the niche. This rather speculative model highlights the importance of the stem cell itself as an active component of the niche, and the role of the niche as a structural unit that concentrates stem cell modulatory factors.

Whereas the Wnt signalling pathway is important for stem cell self-renewal in the intestine and blood, it is used to direct tissue-specific differentiation in other stem cell systems. For example, in the mammalian epidermis, Wnt signalling appears to have a complex role in the differentiation of hair follicle precursors, rather than self-renewal of the multipotent stem cells in the follicular bulge[48–50] (FIG. 2). In the hair follicle, bulge stem cells express high levels of Wnt signalling inhibitors[51,52]. Furthermore, excessive activation of Wnt signalling can accelerate the hair cycle[53] and promote the growth of new follicles, eventually leading to skin tumours[48]. Likewise, in skeletal muscle, Wnt signalling promotes terminal differentiation and fusion of proliferating myoblasts[54], and also has a newly appreciated age-dependent role in determining the balance between myogenesis and fibrosis in injured muscles[19,55].

In addition to secreted protein factors, small molecules and ions can provide important signals in stem cell niches. In the bone marrow, high local concentrations of Ca^{2+} appear to facilitate the localization of HSCs adjacent to osteoblasts at the endosteum[56]. Likewise, the hypoxic microenvironment of HSC niches in the bone may be important for limiting the exposure of HSCs to reactive oxygen species, which appear to induce an oxidative stress response that leads to HSC dysfunction[57]. Thus, multiple soluble factors and small molecules that impinge on stem cell function can be concentrated within the niche such that their activities can be integrated with additional inputs to determine appropriate stem cell responses to physiological stimuli.

Cell adhesion. Physical attachment to supporting stromal cells or to a basal lamina is also important for regulating stem cell behaviour and helps to maintain stem cells within the niche, in close proximity to self-renewal signals. Adherens junctions are cell–cell contacts that are formed by homotypic interactions between transmembrane proteins called cadherins. The loss of cadherin function specifically within germline stem cells (GSCs) in the fly ovary or testis disrupts adherens junctions between stem cells and support cells and causes the subsequent loss of stem cells, indicating that cell–cell adhesion is required for stem cell maintenance in the *D. melanogaster* gonad[27,28] (J. Voog and D.L.J., unpublished observations). Based on expression studies, cadherin-mediated cell adhesion has also been suggested to facilitate HSC association with osteoblasts (through N-cadherin)[13], and has been implicated in determining the correct positioning of muscle satellite cells along the muscle fibre (through M-cadherin)[58]. However, mice lacking M-cadherin show no defects in skeletal muscle development or regeneration[59], and recent studies argue against the involvement of N-cadherin in regulating HSCs; this protein is not detectably expressed by phenotypically identified bone marrow HSCs, and all of the haematopoietic reconstituting activity of normal bone marrow appears to reside in the

Adherens junction
A protein complex that occurs at cell–cell junctions in epithelial tissues. It is usually situated more basally than tight junctions. The primary proteins involved in forming adherens junctions are cadherins.

subset of cells that lack N-cadherin[60]. Thus, it remains unclear which cadherins are specifically important in these stem cell systems and whether functional redundancy with other family members or other adhesion molecules may eliminate the necessity for expression of a particular cadherin protein[59].

Within adult mammalian tissues, high levels of integrin expression can be used as a marker for tissue stem cells, suggesting that attachment to a basal lamina may also be important for holding stem cells within the niche. For example, α6 integrin is highly expressed by basal keratinocytes in the epidermis[34] and has been used as a cell surface marker for enrichment of SSCs in the mammalian testis[61,62]. However, a specific functional role for α6 integrin in stem cell maintenance has not yet been directly demonstrated for these tissues. Likewise, high levels of β1 integrin appear to be characteristic of stem cells in multiple tissues, including those within the interfollicular epidermis, multipotent stem cells within the follicular bulge region of the outer root sheath[34,63], blood-forming HSCs in the bone marrow[64], and self-renewing skeletal muscle stem cells in the satellite cell niche[65]. However, the specific importance of adhesion that is mediated by β1 integrin for stem cell maintenance varies in these different tissues.

Targeted disruption of β1 integrin in cells within the follicular bulge severely impairs the proliferation of precursor cells that contribute to the interfollicular epidermis, hair follicle and sebaceous glands[63]. Conversely, animals in which deletion of β1 and β7 integrins was induced specifically in the adult haematopoietic system maintained appropriate retention of haematopoietic precursors in the bone marrow and showed mainly normal overall haematopoietic function, suggesting that HSC activity is not obligately regulated by these integrins[66]. Instead, other adhesion receptors in the blood system, including membrane-bound steel factor (SLF), c-kit and CXCR4, appear to mediate HSC retention in the niche[67–69]. Analogous loss-of-function experiments to test for a specific role of β1 integrins in mediating stem cell maintenance in other tissues have not been performed. Thus, although cell adhesion is a frequently conserved feature of stem cell maintenance in supportive niches in both mammalian and non-mammalian organisms, it is clear that the specific types of junctions and cell adhesion molecules involved can differ among different stem cell niches, perhaps allowing for more specialized, tissue-specific functions.

Mechanical inputs. In addition to the importance of cell adhesion molecules in retaining stem cells in the niche, stem cell adhesion to cellular and ECM components of the niche also provides important mechanical signals that can have a profound impact on stem cell function. In particular, the relative elasticity or stiffness of the microenvironment can directly modify stem cell differentiation decisions. In one intriguing study, *in vitro* culture of mesenchymal stem cells (MSCs) on a relatively elastic substrate, similar to brain tissue, was shown to promote neural differentiation, whereas culture on a rigid substrate, similar to bone, favoured osteoblast differentiation[70]. MSC culture on a substrate of intermediate stiffness prompted differentiation in the skeletal muscle lineage. Significantly, although the effects of matrix elasticity seemed to be able to initiate or guide lineage commitment, they were integrated together with other differentiation signals provided by soluble factors and could be altered or reversed by these factors in a temporally dependent manner[70]. Although these data have yet to be extended to *in vivo* models, they are nonetheless provocative, suggesting that *in vivo* alterations in matrix elasticity — induced by damage, disease or ageing, for example — could have a profound impact on the cell fate potential and regenerative activity of tissue stem cells. In addition, when considering strategies for the establishment of *ex vivo* niches, these data clearly highlight the importance of establishing appropriate physical and mechanical properties within these synthetic microenvironments.

Spatial cues. The precise topographical organization of stem cells with respect to the surrounding support cells can have an important role in maintaining appropriate stem cell numbers. Polarized attachment to support cells or to the ECM through junctional complexes, or asymmetrically localized factors within the niche, can provide cues that orientate stem cell division and/or specify different cell fates for stem cell progeny. This phenomenon has been best studied in the *D. melanogaster* ovary and testis. In these tissues, direct visualization of GSCs within the niche has revealed that, on cell division, one pole of the mitotic spindle in each GSC is orientated towards support cells, such that the daughter cell that remains within the stem cell niche retains stem cell identity, whereas the daughter cell that is displaced outside of the niche and away from self-renewal signals initiates differentiation[25,26]. Orientated stem cell divisions have also been described in the mammalian epithelium[71,72] and skeletal muscle[42]. Orientation of the mitotic spindle in the developing epidermis appears to be controlled by a mechanism similar to the one that specifies asymmetric division of *D. melanogaster* neuroblasts, which is based on asymmetric localization of a protein complex containing the PAR3 homologue Bazooka, Inscutable and Partner of Inscutable (PINS–LGN)[72] (reviewed in REF. 73). The mechanism(s) that orientates muscle satellite cell division remains unknown. As additional mammalian stem cells are definitively identified *in vivo* within their corresponding niches, such as those in the seminiferous tubules, bone marrow, follicular bulge and intestinal crypts, it will be interesting to determine whether the division of other tissue stem cells is similarly spatially orientated and, if so, whether conserved or unique mechanisms facilitate these orientated divisions.

Home alone. Although the current literature suggests that most stem cells require association with supportive stromal cells for proper function, some stem cells have been found within specific anatomical locations that appear to lack such support cells. One example is the ISCs in the midgut of adult *D. melanogaster*, which maintain the intestinal epithelium and generate both polyploid enterocytes as well as hormone-producing enteroendocrine cells[74,75]. ISCs reside along the basement

Cadherin
One of a family of transmembrane proteins that form homodimers in a Ca^{2+}-dependent manner with other cadherin molecules on adjacent cells.

Neuroblast
A stem cell that is derived from the neural ectoderm (neurectoderm) and produces cells that subsequently differentiate into neurons.

Box 1 | **A niche for cancer stem cells?**

Classic descriptions of cell transformation and tumorigenesis often cite inappropriate overproliferation and loss of contact inhibition as the hallmark properties of malignant cells. Because niche cells normally limit or control stem cell division, these data argue that loss of input from the niche may permit overproliferation of stem cells, which could predispose to transformation. Thus, in light of the fact that cancers are now increasingly recognized as diseases that are maintained by self-renewing cancer stem cells (CSCs; reviewed in REF. 113), this model suggests that independence from niche requirements could distinguish tumour-propagating CSCs from their normal counterparts.

By contrast, additional evidence supports an alternative model whereby direct support from specialized CSC niches may be involved in tumour initiation and/or is essential for tumour maintenance. In one compelling example, Parada and colleagues made the surprising observation that, in a mouse model of neurofibroma induced by inactivation of the tumour suppressor NF1 in glial cells, haploinsufficiency of NF1 in non-neural cell types of the tumour microenvironment actually promotes tumour development, partly by recruitment of functionally altered mast cells, which provide trophic factors to support tumour growth[21,22]. In addition, studies using mouse models indicate that specialized non-neoplastic support cells may act as beacons for the recruitment of metastatic cells in the establishment of secondary tumours at distal sites[114]. Furthermore, expression profiling of stromal cells that are associated with human basal cell carcinomas demonstrated that tumour-associated stroma, but not stroma associated with non-tumour skin, expresses secreted factors that block the differentiation of epithelial cells within the tumour[23]. Thus, strong evidence supports multiple functions of the tumour microenvironment in promoting and sustaining abnormal cell growth in the context of malignancy, and further encourages the novel investigation of the CSC niche as a potential new target for cancer therapy (see also BOX 2).

membrane within clusters or nests of 2–3 basally located diploid cells that are interspersed between polyploid enterocytes. Analysis of mitotic spindle orientation in dividing ISCs indicates that these stem cells divide non-randomly, such that the daughter ISC that remains adjacent to the basement membrane remains an ISC, while the daughter cell that is displaced differentiates to form an enteroblast. Asymmetric division of ISCs is mediated by the Notch signalling pathway. Although all cells in the stem-cell-containing nests are Notch$^+$, only the ISC directly contacts the basement membrane and stains positive for the Notch ligand Delta. Interestingly, Notch signalling is activated exclusively in the daughter enteroblast, rather than in the ISC. Therefore, it appears that ISCs signal through Delta to activate Notch target genes in enteroblasts[76]. Uncovering how Notch signalling is blocked within the ISC to facilitate this asymmetric division is likely to reveal new paradigms for how stem cell self-renewal and maintenance is regulated.

Establishment and turnover of niches

Given the number of components and complexity of interactions within the stem cell niche, it is clear that the formation and activity of niches must be carefully regulated to appropriately control stem cell number and behaviour. In many systems, niches appear to form at discrete developmental times, and their appearance often enables the establishment or recruitment of stem cells at particular anatomic locations. Significantly, once formed, these niches respond dynamically to homeostatic and regenerative cues and can exhibit substantial physiological alterations that affect how they interact with the stem cells they support.

Establishment. The establishment of stem cell niches may proceed by at least two distinct mechanisms. First, niches may arise during development from heterologous cell types, and may stably exist whether or not stem cells are present to occupy them. In the *D. melanogaster* ovary and testis, the somatic component of the gonad (including cells that will ultimately contribute to the niche) forms in the absence of GSCs[77,78]. In the mammalian testis, Sertoli cells support many aspects of spermatogenesis, including SSC self-renewal. Similar to the situation that occurs in the *D. melanogaster* gonad, Sertoli cells are present and maintained even in aspermic testes (such as those of c-kit mutant (W/W^v) mice). However, despite the absence of germ cells in these testes, Sertoli cells remain fully competent to support spermatogenesis, as demonstrated by restored fertility following SSC transplantation[79,80]. Interestingly, in mice lacking the c-kit ligand SLF (which are infertile due to a defect in Sertoli cell support of SSC differentiation), transplantation of normal Sertoli cells restores niche function and fertility, suggesting that SSCs can actually be maintained in the absence of these niche cells[81].

Second, stem cells and the support cells that interact with them may co-develop, with the emergence of each being dependent on proper specification, localization and interactions with the other. This scenario is dramatically demonstrated in transplantation studies of mammalian epidermal stem cells from the follicular bulge region. When purified follicular bulge stem cells and differentiated keratinocytes were transplanted together onto the wounded dorsum of hairless nude mice, the transplanted cells generated all epidermal lineages, including large tufts of stem-cell-derived hair and new stem cell niches within the bulge region of donor-derived hair follicles in the host skin[82]. Similarly, in skeletal muscle, the same embryonic precursors that delaminate from the somites and mediate formation of skeletal muscles in the limb also give rise to muscle satellite cells[83–85], which become encased beneath the basal lamina of mature myofibres and are maintained as muscle-resident myogenic stem cells. Moreover, muscle regeneration, mediated by adult muscle satellite cells, involves both reformation of mature myofibres and re-seeding of muscle stem cells in the regenerated myofibre niche (reviewed in REF. 86). Thus, in both embryogenesis and adult regeneration, the muscle stem cell niche is formed from the same precursors that generate muscle stem cells themselves.

Finally, several tissue stem cell populations, such as HSCs and primordial germ cells (PGCs), encounter multiple niches throughout development that could be customized to support symmetric versus asymmetric divisions; to facilitate rapid proliferation or impose stem cell quiescence; or to bias differentiation of progenitor cells towards one particular lineage (discussed below). In developing mice, HSCs appear sequentially in the yolk sac, dorsal aorta, placenta, fetal liver, spleen and ultimately the bone marrow, which serves as the predominant site of haematopoiesis into adulthood (reviewed in REF. 87). Interestingly, in this progression, it appears that the development of each niche generally precedes seeding with stem cells. Because HSCs are

Mast cells
A haematopoietic lineage cell that is rich in cytoplasmic granules that contain protein mediators, such as histamine, which are released on cell activation. Mast cells are found in many tissues and are implicated in allergy and host defence.

Niche cell
A cell that interacts with a stem cell in a defined anatomical microenvironment (niche). Niche cells can also be referred to as 'support cells' and /or 'supporting stromal cells'.

Primordial germ cell
An embryonic cell that serves as a precursor for the germline (egg and sperm).

Box 2 | **Modulating the niche for therapy**

Several intriguing studies now support the notion that stem cell activity may be modulated indirectly by specifically targeting niche cells. For example, in an elegant series of proof-in-concept experiments, Adams *et al.*[115] recently demonstrated that hormonal treatments that stimulate activation of the osteoblastic niche could increase the number of haematopoietic stem cells (HSCs) *in vivo*. Therefore, such treatments can be used therapeutically to increase the number of HSCs that can be collected for transplant, to enhance the expansion of these cells immediately after transplant, and to protect animals from haematotoxins[115]. Likewise, recent studies using parabiotic mice suggest that changes in the skeletal muscle microenvironment that accumulate with age are regulated by systemic signals that tip the regenerative balance in old muscle to favour fibrosis over muscle regeneration[17,19]. Significantly, treatment with Notch agonists[17] or Wnt antagonists[19] seems to revert these alterations in the niche and rejuvenates muscle repair function. Finally, frequent association of an altered stromal microenvironment with primary and metastatic tumours[24,114] may actually collaborate with intrinsic genetic and epigenetic changes in tumour stem cells to promote tumorigenesis[22,23]. Therefore, directly targeting the tumour cell niche, or preventing the access of tumour cells to their niche[116], could reverse or delay tumour progression and thus provide a novel cancer therapy.

Taken together, these findings have significant implications for the design of new approaches to manipulate stem cell activity for therapy, and suggest that appropriate *in vivo* modification of niche cells may be useful. For example, modification of niche cells enhances the proliferation and function of endogenous stem cells, facilitates the engraftment and expansion of transplanted stem cells, influences the cell fate decisions of differentiating stem cells, and/or inhibits proliferation or promotes apoptosis of tumour-propagating cancer stem cells (FIG. 3). These possibilities are likely to open a wide range of new therapeutic opportunities in regenerative medicine, and may have particular relevance for halting or reversing age-related deficits in tissue function, which appear in several tissues to result from extrinsically regulated deterioration of stem cell activity.

constantly present in the fetal circulation[88], this could indicate that the formation of appropriate niches is the rate-limiting step in the seeding of HSCs into these tissues. Conversely, the developmentally timed disappearance of HSCs from tissues such as the liver may reflect a loss of niches at these sites[88]. Alternatively, developmentally timed seeding of haematopoietic organs by HSCs may result from sequential acquisition — induced by exposure to the 'current' niche — of homing or adhesion receptors that are necessary for localization in the 'next' site[89,90]. This hypothesis would be consistent with data suggesting that sequential transition to or through each of these distinct anatomical compartments may provide important signals that are necessary for the complete maturation of HSCs[60,89,91].

Similar to HSCs, PGCs (the embryonic precursors of the germ line) are formed at an anatomical site that is distinct from their final resting place in the fully developed organism. In the mouse, PGCs are specified from cells of the proximal epiblast and must accomplish a complicated and developmentally timed traverse through the developing organism, passing sequentially through the primitive streak, definitive and visceral endoderm, allantois, hindgut and dorsal mesentery to arrive at the genital ridges. Interestingly, this carefully orchestrated migration appears to be regulated partly by chemotactic proteins such as CXCR4–SDF1α and partly by anatomic localization of PGC survival factors, such as c-kit–SLF, because inhibition of apoptotic PGC death results in ectopic accumulation of PGCs at inappropriate locations[92–94].

Niche turnover. Given that the availability of niches in many systems may control the number of stem cells, mechanisms that determine the number of niches are likely to have a direct impact on stem cell activity in a given tissue. In general, little information is available regarding how the number of niches is determined, how the niche itself is maintained after it is established, or how often the cellular components of niches may be replaced. Significantly, the dynamics of niche cell turnover may vary from tissue to tissue or at different stages of development. However, in several systems, a decline in niche function or in the total number of niches may lead to the subsequent loss or deregulation of tissue stem cells (BOX 1). The potential importance of niche dysfunction is particularly highlighted by recent data suggesting that there is a significant microenvironmental input into age-associated deficiencies of stem cell function. Maintenance and regeneration of tissues such as skin, liver, blood and muscle decrease dramatically with age. In some cases, cell autonomous changes have been proposed to have a role in observed decreases in tissue stem cell function[95] (reviewed in REF. 96); however, cell-extrinsic local and systemic changes also contribute to the declining ability of aged stem cells to adequately repair damaged tissues[17,19,20,97,98].

Recent work has directly demonstrated that age-related changes occur within the stem cell niche that could contribute to deficient stem cell number and/or activity in aged tissues. For example, transplantation of SSCs from young, fertile male mice into the atrophied testes of old males failed to yield robust spermatogenesis or increased testis weight, indicating an age-related decrease in the ability of the stem cell niche to support colonization and/or self-renewal of transplanted SSCs[99]. Complementary studies showed a 73% decrease in the expression of the cytokine glial cell-line-derived neurotrophic factor (GDNF) in ageing (15–19-month-old), infertile males relative to young (2–4-month-old), fertile control males[18]. Because GDNF, which is secreted by Sertoli cells, has been shown to be required for SSC self-renewal and maintenance (TABLE 1), a significant decrease in the levels of GDNF in the testes from old males could provide one mechanism by which ageing of the niche leads to decreased SSC activity and spermatogenesis in old males. These data are similar to the age-related decline in expression of self-renewal signals in key support cells in the *D. melanogaster* male GSC niche, and thus may suggest a conserved molecular mechanism that contributes to ageing of the stem cell niche[20].

Consistent with this hypothesis, changes within the niche also appear to affect stem cell function in aged mammalian skeletal muscle. Transplantation of small amounts of whole or minced muscle tissue from old donors into young recipient muscle beds or, conversely, from young donors into old muscle beds, indicated that muscle regenerative activity is determined in large part by the age of the host microenvironment[100,101]. Surprisingly, the 'age' of the muscle stem cell niche appears to be determined mainly by circulating systemic factors. Exposure of old muscle satellite cells to blood-borne factors rejuvenates their regenerative activity, both *in vivo*

Parabiotic
A term referring to animals that are surgically joined such that they share a common blood circulation.

Glial cell-line-derived neurotrophic factor
(GDNF). A cytokine, often primarily considered to be a neurotrophic factor, that has a role in numerous biological processes including cell survival, neurite outgrowth, cell differentiation and cell migration. GDNF is also secreted by Sertoli cells in the seminiferous tubules, and activates the maintenance of spermatogonial stem cells.

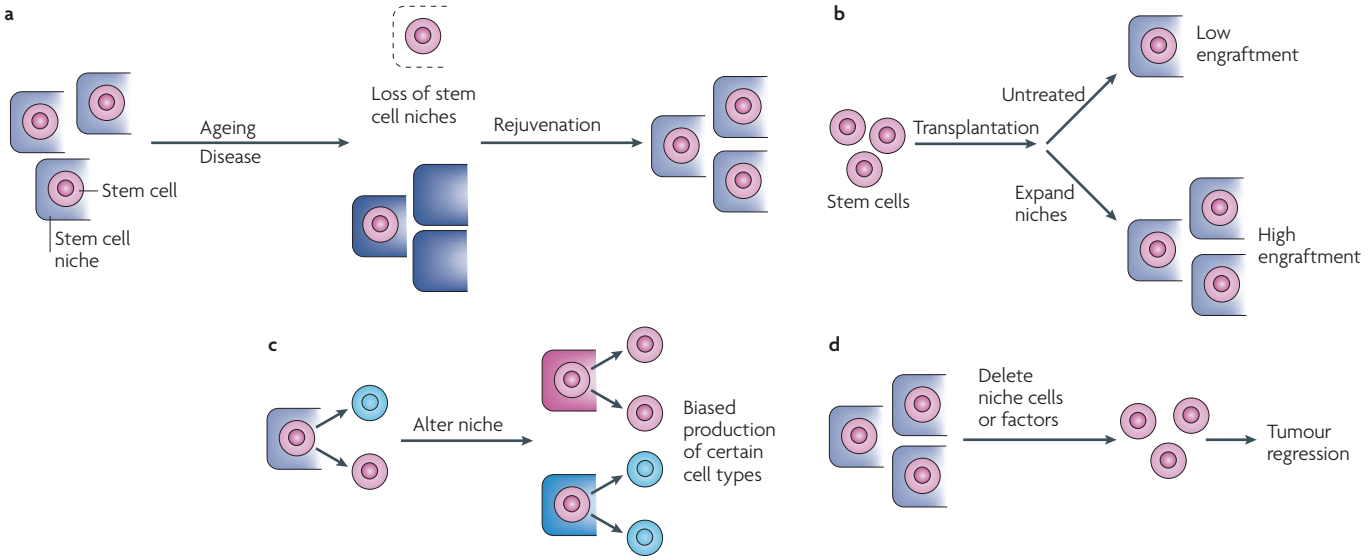

Figure 3 | **Targeting the niche for therapy.** Stem cell deficiency or deregulation contributes to multiple human pathologies, and accumulating evidence suggests that therapeutic targeting of the stem cell niche may provide a novel and effective strategy for improving treatment of these disorders. **a** | For example, correction of ageing- or disease-associated alterations in the niche could be used to boost endogenous stem cell number or function, and thereby improve tissue function[17,19,115]. **b** | Likewise, enhancing supportive niche function during transplantation could improve the efficiency of engraftment or accelerate stem cell reconstitution, perhaps reducing the number of stem cells needed for effective tissue reconstitution[115]. **c** | In addition, because the niche can have an important role in influencing stem cell fate decisions[19,70], as well as promoting stem cell self-renewal, appropriate modification of signals from the niche could be used to alter the outcomes of stem cell differentiation to favour production of a needed cell type or inhibit production of a detrimental one. **d** | Finally, in light of accumulating evidence suggesting that tumour-propagating cancer stem cells are dependent on signals from their niche[22,23,114], just like their non-malignant counterparts, therapeutic ablation of components of the cancer stem cell niche could provide a novel strategy to remove tumour support factors, and thus achieve cancer remission.

and *in vitro*, whereas conversely, exposure of young satellite cells to old serum inhibits their myogenic potential, favouring instead fibrosis and scar formation[17,19].

Flexibility and function

Just as stem cells in different tissues are differently regulated in response to diverse demands for cell replacement, the niches that support these cells exhibit a diversity of functions to provide developmental and homeostatic cues that are appropriate to each tissue. For example, in many systems, such as the intestine and epidermis, stem cells must function continuously to replenish mature cells that normally exhibit a finite lifespan. In these systems, the niche must supply appropriate signals to balance stem cell self-renewal and differentiation to maintain the ongoing production of specialized cells without catastrophic depletion of the stem cell pool. By contrast, in other tissues such as skeletal muscle, the mature progeny of stem cells (muscle fibres) are long-lived, and typically require replacement only when damaged by injury or disease[102–104]. In this case, the niche must provide these facultative stem cells with maintenance and inhibitory signals that promote their survival and prevent their differentiation under steady-state conditions, while simultaneously maintaining responsiveness to regenerative cues so that these stem cells can be mobilized into action when needed. Finally, in some systems, such as the blood, both functions are needed because HSCs must not only maintain daily blood cell production, but must also respond robustly to expand primitive precursor cells following haematopoietic insult[105].

Exactly how the niche effects the regulated conversion from homeostatic to regenerative modes of stem cell maintenance and self-renewal is still unclear. However, this could involve the induction of or recruitment to alternative niches, programmed alteration of existing niches, or both. Thus, stem cell niches must be dynamic enough to provide proper developmental and homeostatic cues to regulate stem cell behaviour in a tissue-specific manner, and in response to various physiological stimuli and pathological conditions. Interestingly, the number of somatic support cells is expanded in the absence of GSCs in the *D. melanogaster* gonad, which results in an apparent expansion of the stem cell niche[77,78]. Furthermore, work in the *D. melanogaster* ovary has demonstrated that stem cell niches that are depleted of endogenous stem cells maintain the ability to signal to and support ectopic proliferation of incoming cells, indicating that empty niches may be capable of promoting self-renewal, proliferation and/or survival of cells that do not normally reside within that niche. Increases in the number of support cells have been induced experimentally in the mammalian blood system, using genetic or pharmacological approaches to expand bone-lining osteoblasts. Osteoblasts provide at least one of the niches that are important for HSC function (TABLE 1), and induced expansion of osteoblasts *in vivo* causes concomitant expansion of HSCs[13,29] (BOX 2; FIG. 3). These data support the notion that stem cell niches

are dynamic, because the number of support cells and available niches appears to respond to complex physiological cues as well as the presence or absence of the endogenous stem cell pool.

Lessons from the haematopoietic system. As indicated above, many stem cells exhibit developmental or contextual changes in their activity and function, and these may be reflected in differences in the niches that they occupy. This paradigm is particularly exemplified by the haematopoietic system, in which the primary site of blood cell production changes sequentially by transition to multiple anatomical locations before settling ultimately in the bone marrow just before birth. Interestingly, in addition to their localization, the cell fate potential of HSCs also changes during development, with several blood cell lineages arising during prenatal haematopoiesis that cannot be generated by adult HSCs ($V\gamma5^+$ T cells[106], for example).

Fetal and adult HSCs also exhibit striking differences in their cell surface marker expression and proliferative activity[107,108]. In the mouse, the transition of HSCs from fetal to adult properties occurs within the first few weeks after birth[47,91,108], and appears to involve an intrinsically timed developmental reprogramming[109] that is associated with loss of expression of the DNA binding factor SOX17 within HSCs[47]. SOX17 is required for the survival of fetal and neonatal HSCs, but is dispensable for adult HSC survival[47]. Precisely how the transition from $SOX17^+$ fetal-type HSCs to $SOX17^-$ adult-type HSCs is orchestrated remains unclear, but it is possible that this maturation is initiated or facilitated by exposure of HSCs to distinct microenvironmental signals that are induced soon after birth. This hypothesis, which remains to be tested experimentally, would suggest that distinct functional properties of different stem cell niches at different developmental times direct developmental stage-specific HSC properties and specification of distinct blood cell lineages.

Similarly, even in the adult blood system, multiple niches for HSCs may exist (including osteoblastic, vascular and perhaps others) and might provide distinct regulatory functions to balance self-renewal[13,29,110] and differentiation[111], leading to the production of mature blood cells. The difficulty to date in deciphering the relative physiological importance of distinct HSC niches arises partly from the fact that studies of HSC niches *in vivo*, even in adult animals, are particularly challenged by the unusual migratory nature of blood-forming HSCs. Using parabiotic mice, we previously made the surprising observation that adult HSCs constitutively recirculate under normal physiological conditions[30]. These cells clearly pass from the bone marrow into the bloodstream, and can return to the marrow to re-engraft and seed ongoing haematopoiesis (FIG. 1). Interestingly, HSCs also appear to traffic from the bloodstream into peripheral non-haematopoietic tissues, where they may participate in local immune or inflammatory responses, or may pass back into the circulation through the lymphatic system[112]. Estimations of the normal flux of HSCs in the body[30] suggest a surprisingly high magnitude of HSC trafficking in normal animals, which makes it difficult to infer the primary function of a niche (that is, does it promote HSC self-renewal, quiescence, differentiation or migration?) solely by direct visualization of its interaction with HSCs *in situ*. Future studies coupling high resolution *in vivo* microscopy, unambiguous niche cell isolation, and direct functional or genetic indicators of HSC cell fate decisions will be needed to clarify these important issues.

Conclusions

Stem cell niches are complex, interactive structures that integrate local and systemic signals for the positive and negative regulation of stem cell activities in a spatially and temporally defined manner. The component 'parts list' for niches is extensive, including cellular and acellular entities, soluble and membrane-bound signalling molecules, mechanical and chemical inputs, and directional as well as feedback control. Recently, great strides have been made in identifying the control circuits that mediate stem cell interactions with the niche at a molecular level. These studies have revealed a striking conservation of function and, in some cases of the molecular effectors of these functions, among stem cell niches. In addition, advances in imaging technology and the identification of stem cell markers have substantially enhanced the ability to visualize stem cells *in situ* within the niche, revealing new insights into the anatomical and structural organization of these compartments. With these tools in hand, the field is now poised to answer several questions that are of fundamental importance to stem cell biology. For example, what is the rate of turnover of niches, and how does this affect stem cell function? How are different signals balanced and integrated in the niche? Is movement from the niche necessary for stem cell differentiation in all stem cell systems? How (and why) do stem cell niches change in the context of disease and ageing? The answers to these and other questions will move us closer to achieving the complex, multidimensional understanding of stem cells and their niches that will be required to enable recapitulation of these native microenvironments outside the body, as well as to direct *in vivo* manipulation of the niche to modulate endogenous stem cell function. Such abilities will yield a more sophisticated knowledge of tissue function and will facilitate new and improved stem-cell-based therapies.

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DATABASES

UniProtKB: http://beta.uniprot.org/uniprot
c-kit | CXCR4 | DKK1 | LGR5 | SLF | SOX17

FURTHER INFORMATION

D. Leanne Jones's homepage: http://www.salk.edu/faculty/faculty_details.php?id=64

Amy J. Wagers's homepage: http://www.joslinresearch.org/PINet/InvestigatorDetail.asp?InvestigatorID=85

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