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Nat Biotechnol. Author manuscript; available in PMC 2015 August 01.

Published in final edited form as:

Nat Biotechnol. 2014 August ; 32(8): 795–803. doi:10.1038/nbt.2978.

Modulating the stem cell niche for tissue regeneration

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Abstract

The field of regenerative medicine holds considerable promise for treating diseases that are currently intractable. Although many researchers are adopting the strategy of cell transplantation for tissue repair, an alternative approach to therapy is to manipulate the stem cell microenvironment, or niche, to facilitate repair by endogenous stem cells. The niche is highly dynamic, with multiple opportunities for intervention. These include administration of small molecules, biologics or biomaterials that target specific aspects of the niche, such as cell-cell and cell–extracellular matrix interactions, to stimulate expansion or differentiation of stem cells, or to cause reversion of differentiated cells to stem cells. Nevertheless, there are several challenges in targeting the niche therapeutically, not least that of achieving specificity of delivery and responses. We envisage that successful treatments in regenerative medicine will involve different combinations of factors to target stem cells and niche cells, applied at different times to effect recovery according to the dynamics of stem cell–niche interactions.

Regenerative medicine has been defined as the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage or congenital defects (http://report.nih.gov/NIHfactsheets/ViewFactSheet.aspx?csid=62&key=R#R). Stem cells are the focus of many applications in regenerative medicine because of their extensive ability to self-renew and to generate differentiated progeny[1]. There are three broad categories of stem cells. Most adult tissues have resident stem cells that are responsible for maintaining that tissue; these cells have been best characterized in tissues that have a rapid rate of cell turnover, such as the blood, epidermis and intestine. Embryonic stem cells are derived in culture from pre-implantation embryos and are referred to as pluripotent because

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COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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they have the ability to differentiate into all cell types in the body. Finally, pluripotent stem cells can be generated by reprogramming adult cells through the introduction of a small number of specific genes; these cells are known as induced pluripotent stem cells (iPSCs).

A central strategy in regenerative medicine is to treat patients by transplanting stem cells or their differentiated derivatives[2]. Transplantation of hematopoietic stem cells (HSCs) obtained from whole bone marrow, peripheral blood or umbilical cord blood provides a paradigm for other forms of cell therapy. HSCs donated by healthy individuals are matched as closely as possible to the recipients to minimize immune rejection. In this way, HSCs have been used for many therapeutic applications, including treatment of genetic blood disorders, such as thalassemia, immunodeficiencies or metabolic diseases, and restoration of the hematopoietic system of cancer patients after chemotherapy. Other validated cell therapies include transplantation of cultured sheets of autologous epidermal or corneal cells to repair burn injuries, and transplantation of *ex vivo*–expanded autologous chondrocytes to repair cartilage defects[3,4]. These examples involve cells from adult tissues. In addition, cells that have been differentiated from pluripotent stem cells are being tested in early-phase clinical trials for treatment of spinal cord injuries and various types of blindness[5–7]. Other experimental cell therapies include transplantation of autologous cells after genetic correction or modification (gene therapy) and the use of mesenchymal stem cells to modulate graft-versus-host disease, to augment HSC engraftment in allogeneic stem cell transplantation or to stimulate regenerative responses in heterogeneous tissues.

In principle, the future of regenerative medicine through cell transplantation is bright. Whereas previously it was only possible to transplant cells that could be harvested from accessible tissues, such as blood or skin, the ability to direct embryonic stem cells or iPSCs to differentiate into inaccessible or rare cell types means that potentially any cell type in the body can now be replaced. And with the advent of iPSC technology, patients can be treated with their own cells, avoiding the problems of immune rejection. Nevertheless, in practice, cell transplantation does have a number of limitations. Autologous treatments, whether with adult cells or iPSCs, are inherently more expensive and labor intensive than pharmaceutical interventions, as they require specialized facilities for cell collection, expansion, quality control and transplantation. In the case of iPSC-based treatments, there are still unaddressed concerns over safety, not least because of the capacity of iPSCs to generate teratomas[8]. Generation of banks of allogeneic cells can reduce the cost of scale-up and reduce batch-to-batch variation in cell quality, but the use of allogeneic cells comes with the need for immunosuppression, which can have undesirable effects in the long term. Regardless of cell source, survival of transplanted cells is often poor as a result of the cells being placed in a suboptimal environment, such as a wound or scar. Even in transplantation of autologous cells, the surgical intervention can provoke an innate immune reaction that hampers cell survival[9].

One alternative or adjunct to cell transplantation is to manipulate stem cells *in vivo*, for example, by stimulating them to proliferate or to generate the requisite type of differentiated cells or by introducing gene sequences that correct a pathologic phenotype. This strategy has the advantage that the tissue would be regenerated by the patient's own cells without the need for biopsy, *ex vivo* cell expansion and manipulation, and transplantation. Such an

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approach would avoid the costly manufacturing challenges associated with cell therapies, including characterization and quality control of a living therapeutic and scale-up of cell production to serve large numbers of patients. The question is thus how endogenous tissue repair could be achieved by administration of small mo lecules, biologics, genes, biomaterials or other agents that are less complex than cells.

In this Review we consider the strategy of targeting the stem cell microenvironment, or niche, to make it supportive of endogenous repair. We discuss the different components of the niche and the evidence that it directs cell behavior. We highlight the importance of cell-cell and cell–extracellular matrix interactions, and physical factors such as oxygen content. The picture that emerges is one of a highly dynamic cellular environment with multiple opportunities to intervene and optimize stem cell function.

The stem cell niche

The term ‘niche’ was first used by Schofield in 1978 to explain the variation in the self-renewal ability of apparently pure populations of HSCs following transplantation in mice[10]. He hypothesized that the ability of stem cells to self-renew and retain their identity depends on the environment provided by neighboring, non-HSC cells. He further proposed that the progeny of a stem cell will undergo differentiation unless they can occupy a similar ‘niche’. In the decades since Schofield’s original article, this concept has been extended to encompass other aspects of the stem cell microenvironment[11,12] (work by F.M.W. and colleagues). Key components of the niche include direct interactions between stem cells and neighboring cells, secreted factors, inflammation and scarring, extracellular matrix (ECM), physical parameters such as shear stress and tissue stiffness, and environmental signals such as hypoxia (Fig. 1). These different aspects of the niche are summarized in Box 1. We therefore consider targeting the stem cell niche to include any approach that modulates individual or multiple components of the niche to facilitate regeneration and tissue repair by activating or otherwise manipulating normal stem cell function.

Box 1

Common features of different stem cell niches

By their very nature, niches are unique and specific in their interactions with their cognate stem cell populations. However, it is important to recognize the many features that are shared between most, if not all, stem cell niches.

1. Heterologous cell-cell interactions are invariably present and often exhibit complex, bidirectional signaling that is dependent on tight regulation and often cell-cell contact. For example, both excess[120] and deficient[128] Wnt signaling within the endosteal niche can have deleterious consequences for HSCs. Stem cell niches contain both tissue-specific (e.g., osteoblastic[30]) and seemingly generic (e.g., endothelial[31,129] or stromal[32]) cell populations that have specialized roles in each context.

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2. Secreted and membrane-bound factors such as Wnt, SCF, Notch and chemokines directly bind surface receptors on stem cells to regulate cell fate, self-renewal and polarity[17,33,37,56–58,130].
3. Immunological cells provide dynamic regulation of the niche during inflammation and tissue damage, and this is tightly regulated through the presence of "immune privilege" and evasion from this privilege[36,78].
4. ECM proteins are critical for orientation and structural maintenance of the niche, but importantly provide instructive signals through ligand interaction with integrins expressed on stem cells and may also serve as reservoirs for soluble factors[131] (work by D.A.W. and colleagues).
5. Physical parameters such as shape, stiffness (or elasticity) and blood flow direct stem cell maintenance and differentiation[103,104,106,108].
6. Many stem cell niches have altered environmental characteristics, such as hypoxia, and require tight metabolic regulation to maintain the long-term quiescence and self-renewal of stem cell populations[111,112,114,130].

Numerous studies have highlighted the importance of the niche in modulating stem cell behavior[13], and since publication of Schofield's hypothesis of an HSC niche[10], stem cell niches have been described in a variety of adult tissues, including skin[14], intestine[15–18] and nervous system[19,20]. Figure 2 illustrates the main features of the stem cell niche in the bone marrow, skin and intestine; features common to all of them are shown in Figure 1 and Box 1.

The role of the niche is observed at several levels of resolution, which can be illustrated using the example of the epidermis. At the macro level, the importance of the epidermal niche was demonstrated by placing grafts of autologous cultured epidermis in direct contact with the muscle fascia in patients with extensive burns. Subsequently, engraftment of epidermal tissue was improved by placing it onto cadaveric stroma used to provide temporary coverage of the wound or by first culturing epidermal cells on an extracellular support made of fibrin rather than on tissue culture plastic[21,22]. This demonstrates that the nature of the extracellular matrix that epidermal cells attach to influences graft survival. At the level of individual stem cells, when different subpopulations of epidermal stem cells are disaggregated and used to reconstitute the skin, their differentiation potential is greater than when they are resident in the skin under homeostatic conditions[23]. In addition, the rate of proliferation of epidermal stem cells is dictated, at least in part, by signals such as growth factors and direct cell-cell contacts emanating from terminally differentiated epidermal cells overlying the stem cell compartment[24] (work by F.M.W. and colleagues). The behavior of epidermal stem cells is also profoundly influenced by signals from cells within the dermis, which can occur over short range, as in the case of the dermal papilla at the base of each hair follicle[25] (work by F.M.W. and colleagues), or over longer range, as in the case of skin adipocytes[26,27]. These three cell types can all be considered part of the epidermal stem cell niche. Furthermore, communication between stem cells and niche cells is reciprocal: signals from epidermal stem cells influence differentiation within the dermis, through both short-

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and long-range communication[28,29] (work by F.M.W. and colleagues). One example of signaling at short range is that deposition of the ECM protein nephronectin by a subset of epidermal stem cells provides an adhesive substrate for adjacent mesenchymal cells that subsequently differentiate into smooth muscle cells[28].

These studies of the skin highlight the ability of the niche to regulate stem cell self-renewal and generation of differentiated progeny. Niche signals can act at short or long range and at the level of individual cells or entire cell populations. A detailed discussion of the niche of every tissue is beyond the scope of this Review; rather, we will use examples to explore commonalities between different niches (Box 1) and to discuss specific precedents and opportunities for *in vivo* therapeutic intervention.

Cellular components of the niche

Resident niche cells

In many adult tissues, the stem cell niche contains a variety of cell types, each with a distinct function. This is clearly illustrated in the case of the hematopoietic microenvironment localized in the marrow space in adult bone and comprising a range of different cell types. Osteoblastic[30], vascular[31,32] and neural cells[33], megakaryocytes[34], macrophages[35] and immune cells[36] each have important roles and can be considered to define distinct HSC niches. Currently, controversy surrounds the differential roles of the osteoblastic and perivascular niches and, in particular, whether they have distinct, specialized roles or whether there is coordinated regulation of HSCs and therefore functional overlap[13]. For example, $NG2^+$ peri-arteriolar cells regulate quiescence within long-term HSCs, and this quiescence appears essential for HSC function[32]. Other cells, such as endosteal macrophages, retain HSCs within the niche, and loss of these cells causes mobilization of HSCs out of their supportive microenvironment[35].

In the case of stem cells in the colon and intestine, key niche cell types include the differentiated progeny of the stem cells. In the small intestine, Paneth cells physically co-localize with, and in turn support, intestinal stem cells through secretion of Wnt3a, Notch and epidermal growth factor[16,18,37]. In the colon, stem cells co-localize with their differentiated progeny, the goblet cells, which express c-kit, notch ligands and epidermal growth factor[38]. Thus, discrete niches exist in different parts of the gastrointestinal tract and contribute to tissue homeostasis.

A further concept that could be of practical importance is that experimental ablation of stem cells can result in neighboring cells dedifferentiating to replace them. When germline stem cells are ablated in *Drosophila* ovarioles, neighboring stromal cap cells (niche cells) persist and support the entry of somatic cells into the empty niche where they subsequently proliferate[39]. In mouse skin, laser ablation of hair follicle stem cells leads to repopulation of the niche by neighboring epithelial cells that are able to sustain hair regeneration[40]. In the liver, activation of Notch signaling reprograms hepatocytes to become biliary epithelial cells[41]. The presence of reserve stem cell populations[42] and the reversion of differentiated cells to stem cells regulated in part by the niche[17] have clear therapeutic implications for degenerative diseases. However, at present it is an open question as to whether the

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frequency of dedifferentiation could ever be sufficiently high to be of practical importance in tissue regeneration.

Direct cell contact

Communication between stem cells and niche cells is either direct, through physical interactions, or indirect, through secreted factors that mediate communication between cells that are not in direct contact. Direct contact can be mediated by a range of receptors, including bona fide cell-cell adhesion molecules and receptors with membrane-bound ligands. In the latter category, the Notch pathway stands out as being important in regulating stem cell function in many tissues. In the skin, it is well established that Notch signaling mediates distinct outcomes according to the level of pathway activation and acts both cell autonomously and non–cell autonomously by means of signaling between epidermal cells, fibroblasts and bone marrow–derived cells[43,44] (work by F.M.W. and colleagues). In bone marrow, Notch ligands expressed by sinusoidal cells are essential for HSC self-renewal during recovery from myeloablative injury[45].

In addition to Notch-receptor interactions, a number of other proteins that mediate intercellular communication through direct cell-cell contact are important in the niche. In *Drosophila* testis, the receptor tyrosine phosphatase Lar regulates adhesion between germline stem cells and niche cells[46]. In bone marrow, the cell adhesion molecule E-selectin is expressed by endothelial cells and promotes HSC proliferation[47]. HSC quiescence can be induced by administration of an E-selectin antagonist, which enhances HSC survival following treatment with chemotherapeutic agents or irradiation. Another interesting example is SCF, the ligand for the receptor tyrosine kinase c-kit. SCF is expressed in both soluble and membrane-bound isoforms, and experimental and genetic data suggest that stem cells expressing c-kit (including HSCs, melanocyte precursors and germ cells) have a specific requirement for membrane-bound SCF expressed on marrow stromal cells for their lodgement into the niche[48,49] (work by D.A.W. and colleagues). This pathway may be modulated through a variety of small molecules, such as tyrosine kinase inhibitors[50], and by neutralizing antibodies to c-kit[51].

Secreted factors

Indirect communication between stem cells and niche cells is mediated by secreted factors. In the hematological system, this phenomenon is routinely exploited in clinical practice to modulate the HSC niche *in vivo* (Fig. 3). Mobilization of HSCs from their niche, for example, by using cytokines such as granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF), is widely used to support treatment of hematological malignancy, bone marrow failure and rare genetic disorders (reviewed in To *et al.*[52]). These factors act in a variety of ways, including promoting expansion of HSCs and release of HSC-niche adhesion. The utility of targeting the niche with soluble factors is further illustrated by the finding that activation of the parathyroid hormone (PTH) receptor on osteoblasts by PTH increases HSC number[53]. HSCs do not express the PTH receptor; instead, stimulation of osteoblasts by PTH activates Notch signaling in HSCs[53]. PTH treatment is therapeutically beneficial in several different experimental, clinically relevant mouse models: it increases the number of HSCs mobilized

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into the peripheral blood, protects stem cells from cytotoxic drugs used in chemotherapy and expands stem cells in transplant recipients[54]. The potentially beneficial effect of PTH does not appear to be due to osteoblastic proliferation, as strontium also expands osteoblastic cells but does not alter HSC function[55].

Although the studies with PTH demonstrate that the niche can be targeted with soluble factors, more recent studies show that the effects of a single niche factor differ according to the niche cell that expresses it. Deletion of Cxcl12 in different HSC niche cells has different outcomes[56,57]. Its deletion from perivascular stromal cells depletes HSCs and mobilizes them into the circulation, whereas deletion from osteoblasts depletes early lymphoid progenitors but not HSCs and does not lead to HSC mobilization. Deletion of Cxcl12 from endothelial cells has relatively little effect on the HSC compartment. These studies show that modulating a single secreted niche factor has different outcomes depending on which niche cell is producing it and highlight the potential difficulty of achieving therapeutic benefit by targeting a single component of the niche.

A signaling pathway that is involved in the regulation of almost all stem cell populations is the Wnt pathway[58]. Modulation of Wnt activity in the stem cell compartment has intrinsic effects both on those cells and on neighboring cells. For example, activation of the Wnt pathway in epidermal stem cells not only expands the stem cell compartment and promotes hair follicle differentiation but also stimulates melanocyte differentiation and reprograms adult dermis to acquire characteristics of neonatal dermis[29,59–61] (work by F.M.W. and colleagues). Different levels of Wnt pathway activation have different effects, both within the epidermis and in the underlying dermis[59,62].

The Wnt pathway is inappropriately activated in a wide range of cancers, and considerable progress has been made in developing drugs that inhibit different parts of the pathway[63]. However, methods for activating the pathway using recombinant Wnt proteins are challenging because the proteins are hydrophobic and difficult to produce in biologically active form[64]. Furthermore, given that Wnt proteins act both on stem cells and niche cells within the same tissue[59,61], localized delivery could be a major issue that is irrelevant in other contexts, such as PTH in the HSC niche. One elegant way to overcome this is to immobilize biologically active Wnt on beads or other inert scaffolds[65]. This enables the application of Wnt protein to modulate juxtacrine signaling, as occurs during normal development[66].

Other self-renewal pathways, such as Hedgehog signaling, are also important in the normal[67] or cancer-stem-cell niche[68], and novel Hedgehog inhibitors have reached early-phase clinical trials, with promising results in the treatment of medulloblastoma and basal cell carcinoma[69]. Basal cell carcinoma is believed to develop from epidermal stem cells and, not surprisingly, a side effect of inhibiting Hedgehog signaling in this disease is hair loss[70]. Therefore, as previously noted for Cxcl12, the challenge of targeting the niche therapeutically by secreted factors is how to achieve specificity in terms of which cells respond.

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Metastatic malignancy provides a compelling argument that manipulation of the niche for therapeutic ends is feasible[71]. Endogenous soluble factors, such as transforming growth factor, matrix metalloproteinase, tumor necrosis factor or receptor activator of nuclear factor kappa-B ligand, derived from circulating bone marrow cells create a pre-metastatic niche at distal sites (e.g., the lungs) that supports the engraftment and metastasis of cancer stem cells[72]. Additionally, in some hematological cancers such as leukemia or multiple myeloma, cancer stem cells secrete CCL3 or other paracrine factors that lead to remodeling of normal niches through bone loss and increased osteoclastic activity[73].

The secreted factors discussed so far are proteins that are expressed during normal tissue development, homeostasis and repair. A complementary approach, which is potentially easier to scale up and more cost effective, is to screen compound libraries for small molecules that target the niche. Screens for compounds that target stem cells are a very active area of research[74] and, provided that the right assays to determine effects on stem cell–niche interactions are used, there is no reason why similar niche-regulator screens could not be designed[75]. Although we view high-throughput screening approaches with optimism, clinical translation of small molecules identified in this manner remains to be fulfilled, in part explained by the inherent limitations of taking a reductionist, *ex vivo* approach to niche interactions rather than faithfully modeling what is certainly a more complex *in vivo* microenvironment.

In summary, clinical practice in hematology and studies in animal models for tissues other than the blood suggest that new regenerative strategies that involve modifying the cellular components of the stem cell niche could be developed to expand or recreate the stem cell compartment or to change the fate of stem cells and their progeny. A number of strategies can be envisaged, from modulating the factors secreted by niche cells to interfering with direct cell-cell contact or altering the number and type of niche cells (Fig. 3).

The dynamic niche: inflammation and scarring

Although every stem cell niche is dynamic and exhibits cell turnover, it is useful to distinguish between niche cells that are ‘permanent residents’ and cells that occupy the niche in a transient fashion. Permanent residents would include endothelial cells, nerve cells and connective-tissue fibroblasts. The ‘visitors’ would include immune cells and cells that respond to tissue damage, for example, to protect against pathogens or to promote healing.

In contrast to resident niche cells, many cells of the innate and adaptive immune system migrate into and out of tissues. The function of immune cells can be modulated to promote stem cell function. For example, HSCs can be genetically modified to drive tolerogenic expression of antigens, thereby improving the long-term efficacy of HSC transplants[76]. Severe aplastic anemia, a condition in which bone marrow failure is caused by an immune attack on endogenous HSCs, can be effectively treated with anti-thymocyte globulin and immunosuppressive medications[77].

Regulatory T lymphocytes provide immune privilege to the HSC niche[36], and this finding is being exploited in clinical trials to prevent rejection of transplanted organs. Interestingly, mobilized HSCs upregulate surface CD47 expression, which acts to prevent phagocytic

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clearance of these cells[78]. Anti-CD47 antibody–mediated phagocytosis of tumor cells by macrophages is being evaluated as an anti-cancer therapy, and one could envisage that a similar strategy could be used to promote macrophage-mediated clearance of cells that are hindering endogenous tissue repair. Acute brain injury not only causes neuronal cell death but also causes damage to, and death of, niche-resident endothelial cells and macrophages, with resulting generation of reactive oxygen species (ROS). Accordingly, administration of the ROS scavenger, glutathione, promotes meningeal macrophage survival, reduces inflammation and ameliorates brain injury[79].

Tissue injury and scarring represent other aspects of transient stem cell–niche interactions that can be targeted for therapeutic benefit. Fibrosis is an undesirable consequence of repeated injury and repair in a variety of tissues. In the skin, the existence of two different fibroblast lineages has recently been reported[29]. The lineage that mediates the initial wave of wound repair is unable to support hair follicle formation. But both subsets of dermal fibroblasts can be modulated by Wnt signaling, offering a potential route to changing the composition of the niche[29]. In genetically modified mice, Wnt-induced expansion of the fibroblast lineage that is required for hair follicle formation leads to the formation of new hair follicles in skin wounds. In wounded skin, gamma delta (γ/δ) T cells secrete fibroblast growth factor 9, which in turn triggers Wnt expression in fibroblasts and promotes hair follicle regeneration[80]. It remains to be determined whether γ/δT cells communicate selectively with the fibroblast lineage that is required for new hair follicle formation, or whether the T cells are able to confer hair follicle induction ability on other fibroblast populations.

Reducing fibrotic scar formation is a goal in many regenerative strategies, but in some cases, such as in the injured spinal cord, it may actually inhibit repair. Scar tissue is an inappropriate environment for repair over the long term, but immediately after injury it can limit damage. After spinal cord injury, scarring by astrocytes may restrict enlargement of the lesion and axonal loss[81]. In addition, neural stem cell progeny secrete a range of neurotrophic factors that promote neuronal survival[81]. As the example of the spinal cord shows, therapies to increase regeneration by inhibiting the scar niche require further investigation as they could have undesirable effects.

Extracellular matrix

The ECM is a key component of the stem cell niche in almost all tissues, although its composition and the nature of its contact with stem cells vary considerably[82] (work by F.M.W. and colleagues). It has been appreciated for many decades that the ECM not only anchors stem cells but also directs their fate[11]. Many of the intracellular signaling pathways involved in ECM–stem cell interactions have been elucidated[82]. In some cases, the ECM also anchors soluble growth factors, increasing the local concentration of agonists to which target populations in the niche are exposed[83]. For example, adhesion molecules regulate interactions between stem cells, ECM and resident niche cells, and the expression of these molecules may be regulated by secreted factors[84]. The major ECM receptors are integrins, and their functions can be modulated with biologics, such as antibodies, or with small-molecule drugs. Just as with the Wnt pathway, abnormal integrin signaling is linked to

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cancer and other pathologies, including thrombotic diseases and inflammation, and pharmacological inhibitors of integrins are in the clinic[85]. Conversely, activating integrin antibodies are available to promote interactions between the ECM and stem cells[86]. In the case of the epidermis, such activating antibodies can decrease differentiation of stem cells[87] (work by F.M.W. and colleagues).

The interaction of the ECM with stem cells depends not only on its protein composition but also on its physical properties. There is strong evidence that ECM surface topography and bulk stiffness can profoundly influence stem cell behavior[82,88]. These findings are increasingly informing the design of appropriate scaffolds for tissue repair[89]. Considerable progress has been made in the design of porous bioactive scaffolds that support bone regeneration and are resorbable[90]. High-throughput niche screens have demonstrated the synergistic effects of combinations of ECM and soluble factors[91]. Scaffolds can incorporate ECM protein motifs and/or growth factors. They can be used to localize stem cells and soluble molecules, for controlled release of soluble factors and for delivery of niche cells[92,93]. Several examples of the use of artificial scaffolds are shown in Table 1.

One category of disease that is readily attributable to defective ECM–stem cell interactions is epidermolysis bullosa (EB), a family of rare genetic skin blistering disorders[94]. Mutations responsible for different types of EB have been identified, including recessive dystrophic junctional EB (RDEB), which results from a failure to deposit type VII collagen in the basement membrane, and junctional EB, which is characterized by defective production of laminin 5. In one clinical study, junctional EB was corrected by culturing epidermal stem cells from the patient, transducing them with a retroviral vector encoding the missing laminin gene and grafting the gene-corrected cells onto the patient[95].

Although such an approach is potentially feasible for RDEB, studies in mice have suggested a different strategy: transplantation of allogeneic fibroblasts[96] or bone marrow from unaffected individuals. In a clinical trial of whole bone marrow transplantation, there was correction of the basement membrane defect in some patients[97,98]. In another study, a single injection of fibroblasts led to type VII collagen expression that was sustained for several months, with the newly deposited type VII collagen derived from the injected fibroblasts[96]. This illustrates the challenges to identify the most effective mechanism to repair the ECM *in vivo* and to further elucidate the signals from the damaged epidermis that stimulate pathological niche remodeling[99].

One further intriguing feature of EB is the phenomenon of revertant mosaicism, whereby patches of epidermis spontaneously recover and produce the wild-type gene product, leading to healthy, non-blistered epidermis[100,101]. This phenomenon is important for several reasons. One is that if the underlying mechanism can be discovered and stimulated it would lead to new therapies[94]. Another is that iPSCs can be generated from the revertant areas, differentiated into epidermis and then used for grafting the affected regions[102]. Finally, clinical observations indicate that many of the revertant regions, although stable, do not expand over time. If expansion could be stimulated, presumably by modulating the niche, this would offer another avenue for tissue repair.

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Physical factors

Stem cells rely on cues from their physical surroundings—substrate elasticity or stiffness, physical shape and shear forces. These processes have been applied both to improve *in vitro* culture and in an attempt to expand stem cell populations, such as HSCs and skeletal muscle stem cells[103,104], and to various therapeutic contexts. Drugs that alter the balance between physical parameters, such as rigid (e.g., bone) or elastic (e.g., arteriolar, dermal connective tissue), already exist and are in clinical use for conditions such as osteoporosis and metastatic bone disease. Potassium channel openers, such as minoxidil, may act to increase elastic fiber content, thus maintaining niche elasticity *in vivo*[105]. Shear forces and drugs that promote blood flow accelerate the development of zebrafish embryonic HSCs *in vivo*[106], whereas zebrafish and murine mutants that lack blood circulation exhibit reduced hemopoiesis. At the single-cell level, promotion of contractility by nonmuscle myosin-II in HSCs is required for engraftment and niche sensing[107]. Finally, distinct niche topographies induce cytoskeletal deformation on stem cells, and this in turn activates specific downstream signaling pathways and directs differentiation[108,109]. These pathways could be modulated *in vivo* by inhibitors of RHO-GTPase signaling or indirectly through chromatin modifiers such as trichostatin A[110].

Hypoxia and metabolism

Many cell populations, including HSCs and cardiac progenitors, reside in a low oxygen–tension (hypoxic) microenvironment[111], which contributes to their survival and maintenance. Cells in such an environment carry out glycolysis rather than mitochondrial oxidative phosphorylation, and express high levels of hypoxia inducible factor 1α (HIF-1α). Growing a range of different mammalian cell types in culture under hypoxic conditions is beneficial for promoting survival, proliferation and function after engraftment[112]. In the hemopoietic system, the hypoxic environment is required for HSC quiescence and self-renewal, and stabilization of HIF-1α, either through the administration of dimethyl prostaglandin E2 (dmPGE2)[113] or with dimethyloxalyl glycine (DMOG) or FG-4497, improves HSC quiescence and long-term HSC function[114].

Cellular metabolism plays a pivotal role in determining whether a cell proliferates, differentiates or remains quiescent. There is a shift in the balance between glycolysis, mitochondrial oxidative phosphorylation and oxidative stress during the maturation of adult stem cells and during reprogramming of cells to a pluripotent state. This opens the way for novel metabolic or pharmacological therapies to enhance regeneration[115,116]. At present the most tractable applications of the recent insights into stem cell metabolism are to improve culture conditions for *ex vivo* cell expansion and differentiation. Nevertheless, one could envisage the development of drugs that target relevant metabolic enzymes and new technologies to track changes in cell metabolism *in vivo*.

At the level of the whole body, stem cell behavior is affected by factors such as nutritional status, aging[117] and circadian rhythms[8,118]. It remains to be determined whether modulating the effects of these processes on the stem cell niche could have regenerative effects in specific target organs.

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Conclusion

The past 10 to 15 years have witnessed an explosion in our understanding of the way that stem cells interact with their supporting niche, defined as the totality of the stem-cell microenvironment. More recently, tantalizing evidence has emerged in human and animal studies that modulating the stem cell niche can modulate the function of stem cell populations. Table 1 lists examples of this approach that are already approved or are in clinical trials. Niche-directed therapies may eventually be used more broadly in regenerative medicine for chronic degenerative diseases as well as in transplantation medicine and oncology. There are many hurdles on the path to achieving this vision. Efficacy and safety have been demonstrated in humans for restoration of the hematopoietic system, but progress has been slower in other tissues and organs. Challenges include assuring the tissue specificity of any intervention, guaranteeing the quality of repair over the long term and avoiding side effects of treatment such as carcinogenesis. Any therapeutic intervention that modulates critical developmental pathways, such as Wnt, Hedgehog or Notch signaling, may have teratogenic[119] or carcinogenic[120] effects. Although a more liberal ‘therapeutic window’ may be justified in the case of life-threatening conditions such as cancer, the potential for detrimental effects requires particularly careful attention in the context of regenerative therapies for conditions that are less serious or for which alternative therapies are available.

In practice, the most successful regenerative medicine treatments involving endogenous repair will probably be combination therapies. Targeting the niche is complementary to approaches that target stem cells directly, providing substantial opportunities for synergy. One could envisage treatments that involve not only different combinations of factors to target stem cells and niche cells but also applying such factors at different times to effect recovery according to the dynamics of stem cell–niche interactions.

Acknowledgments

We apologize for any omissions due to space constraints. S.W.L. is supported by research funding from the National Health and Medical Research Council, the Leukaemia Foundation of Australia and the Rhys Pengelly Fellowship in Leukaemia Research. D.A.W. is supported by National Institutes of Health DK062757. F.M.W. gratefully acknowledges the financial support of the Medical Research Council and the Wellcome Trust.

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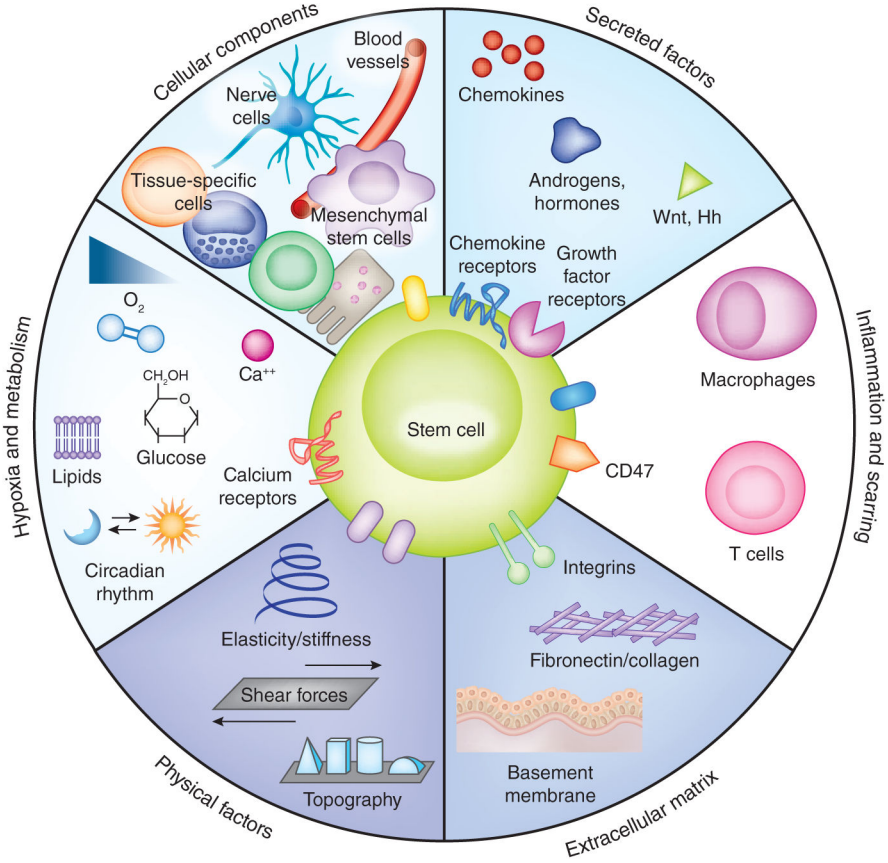

Figure 1.

Composition of the niche. Stem cell niches are complex, heterotypic, dynamic structures, which include different cellular components, secreted factors, immunological control, ECM, physical parameters and metabolic control. These aspects of the niche are described in more detail in Box 1. The interactions between stem cells and their niches are bidirectional and reciprocal.

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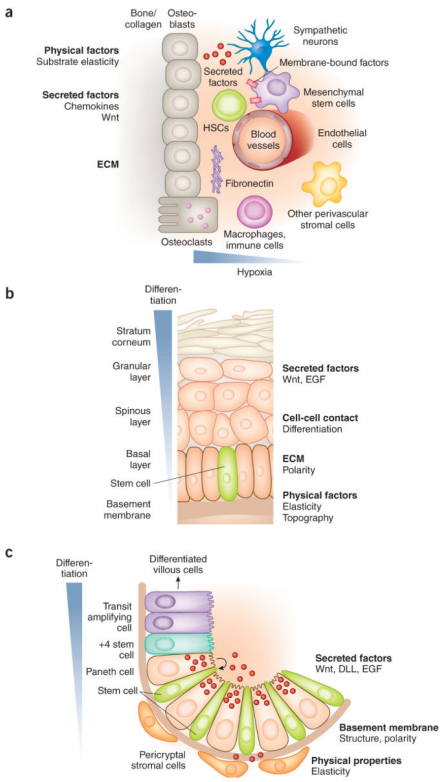

Figure 2.

Representative schema illustrating stem cell niches. (**a**–**c**) Discrete niches that support hematopoietic (**a**), epidermal (**b**) and intestinal stem cells (**c**). **b** adapted from ref. 14 with permission from Elsevier; **c** adapted from ref. 16, Nature Publishing Group.

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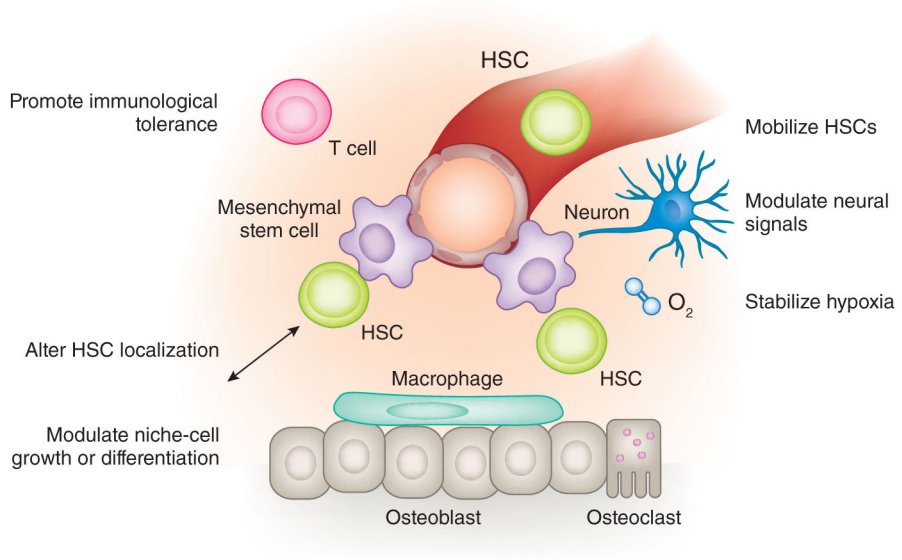

Figure 3.

Manipulation of the hematopoietic stem cell niche *in vivo*. *In vivo* manipulation of HSCs may be achieved by altering constituent niche cells, by administering drugs to alter cellular localization, by disrupting adhesive interactions or by stabilization of nutritional support (e.g., promoting hypoxia). Immune regulation of the HSC niche may be targeted through immunosuppressive medications or in allogeneic transplantation. HSC mobilization is regulated in part by the HSC niche and can be achieved with cytokine growth factors or by blocking adhesion molecules.

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Table 1

Examples of *in vivo*, niche-directed regenerative therapies in current clinical use or in clinical trials

Disease indication	Niche target	Therapeutic approach
Hematopoietic regeneration post-transplantation	Osteoblastic cells	Parathyroid hormone to stimulate osteoblasts (N.B., efficacy was not demonstrated)[121]
Bone marrow failure (severe aplastic anemia)	Secreted growth factors	Thrombopoietin mimetics[122]
	Immune cells	Anti-thymocyte globulin*[77]
HSC mobilization	Niche cells and secreted factors	G-CSF* or GM-CSF*[52]
		AMD3100* (ref. 52)
Spinal cord injury	Hypoxia	Daily, intermittent hypoxia exposure[123]
Bone fracture or excision	ECM, mesenchymal cells, secreted factors	3-dimensional bioengineered scaffolds, mesenchymal stem cells and bone morphogenic protein 2 (NCT01958502, clinicaltrials.gov)
	Physical forces	Low-magnitude mechanical stimulation (NCT019215517, clinicaltrials.gov)
	Scaffolds and secreted growth factors	Scaffolds linked to BMP-2* (ref. 124) or platelet-derived growth factor[125]
Skin damage (e.g., burns, diabetic ulcers, wound excisions)	ECM and scaffolds	Dermal replacement scaffold (NCT02059252, clinicaltrials.gov)
	ECM and growth factors	Platelet-derived growth factor in carboxymethylcellulose gel*[126]
	Vascular niche cells	GM-CSF[127]

Approved therapies are indicated with an asterisk.