Cell Stem Cell
Perspective

The Stem Cell Niche in Regenerative Medicine

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Stem cells are fundamental units for achieving regenerative therapies, which leads naturally to a theoretical and experimental focus on these cells for therapeutic screening and intervention. A growing body of data in many tissue systems indicates that stem cell function is critically influenced by extrinsic signals derived from the microenvironment, or "niche." In this vein, the stem cell niche represents a significant, and largely untapped, entry point for therapeutic modulation of stem cell behavior. This Perspective will discuss how the niche influences stem cells in homeostasis, in the progression of degenerative and malignant diseases, and in therapeutic strategies for tissue repair.

Effective functioning of the body's tissues and organs depends upon innate regenerative processes that maintain proper cell numbers (homeostasis) and replace damaged cells after injury (repair). In many though not all tissues, regenerative potential is determined by the presence and functionality of a dedicated population of stem and progenitor cells, which respond to exogenous cues to produce replacement cells when needed. Understanding how these unspecialized precursors are maintained and regulated is essential for understanding the fundamental biology of tissues. This knowledge also has practical implications, as the regenerative potential of tissue-specific stem and progenitor cells can be exploited therapeutically by transplantation to replenish the stem cell pool, by endogenous manipulation to boost the repair activity of cells already present in the tissue, or through in vitro modeling of development and disease to provide otherwise inaccessible systems for identifying pathological mechanisms and testing the efficacy of newly discovered drugs.

Indeed, the promise of stem cell biology for the development of novel therapeutics has fueled a veritable explosion in studies aimed at using these cells in "regenerative medicine," an emerging field of biomedicine focused on the "repair, replacement, or regeneration of cells, tissues or organs" (Mason and Dunnill, 2008). Yet such strategies ultimately must consider and address biological constraints imposed by both the stem cell itself and the environment, or niche, in which the stem cell is asked to function. In this Perspective, I review existing and emerging evidence suggesting that the stem cell niche represents a particularly attractive and relatively underexploited entry point for the discovery of novel stem cell regulatory mechanisms and the development of new applications in regenerative biology. Several new and exciting studies, in both the hematopoietic (blood-forming) system and solid organs, have highlighted the potential of such approaches. This work likely represents the shallow end of a very deep pool, which upon further investigation will yield new paradigms for understanding and controlling stem cell functions to achieve therapeutically valuable results.

Stem Cells and Their Niches

As the functional units for growth and regeneration in many tissues, stem cells hold a position of significant importance for maintaining proper tissue function. Thus, these cells should be protected as much as possible from damage or loss, while at the same time maintaining sufficient communication with their surroundings to ensure appropriate responsiveness to physiological cues for cell replacement and repair. In many tissues, this balance between protection and interaction appears to be accomplished by maintaining stem cells in a specialized microenvironment, or niche, which provides spatial and temporal cues to support and coordinate stem cell activities (Wang and Wagers, 2011). Stem cell niches have been identified and characterized in many tissues, including the germline, bone marrow, digestive and respiratory systems, skeletal muscle, skin, hair follicle, mammary gland, and central and peripheral nervous systems. Extensive studies in a number of different laboratories have begun to elucidate the critical components of many stem cell niches, which include specific mesenchymal, vascular, neuronal, glial, and inflammatory cell types, diffusible and cell-surface-associated signaling molecules, and physical parameters such as matrix rigidity, shear stress, oxygen tension, and temperature (see Figure 1; reviewed in Bautch, 2011; Ehninger and Trumpp, 2011; Jones and Wagers, 2008; Morrison and Spradling, 2008; Peerani and Zandstra, 2010; Raaijmakers, 2011; Sneddon and Werb, 2007; Voog and Jones, 2010; Wang and Wagers, 2011; Wilson and Trumpp, 2006). In particular, cell-cell interactions within the niche provide structural support, regulate adhesive interactions, and produce soluble signals that can control stem cell function. Stem cell interactions with the extracellular matrix (ECM) provide retention cues, as well as mechanical signals, based in part on substrate rigidity (Engler et al., 2006; Gilbert et al., 2010), which allow stem cells to respond to external physical forces. In addition, the ECM can sequester or concentrate growth factors, chemokines, and other stem cell regulatory molecules by binding both locally and systemically produced factors within the niche (Yamazaki et al., 2011). The close association of many stem cell types with the vasculature and nervous system allows for modulation of stem cell responses by metabolic cues and circadian rhythms (Kiel et al., 2005; Méndez-Ferrer et al., 2008, 2009, 2010), and provides a conduit through which inflammatory and immune cells, as well as humoral factors, can be delivered to the niche

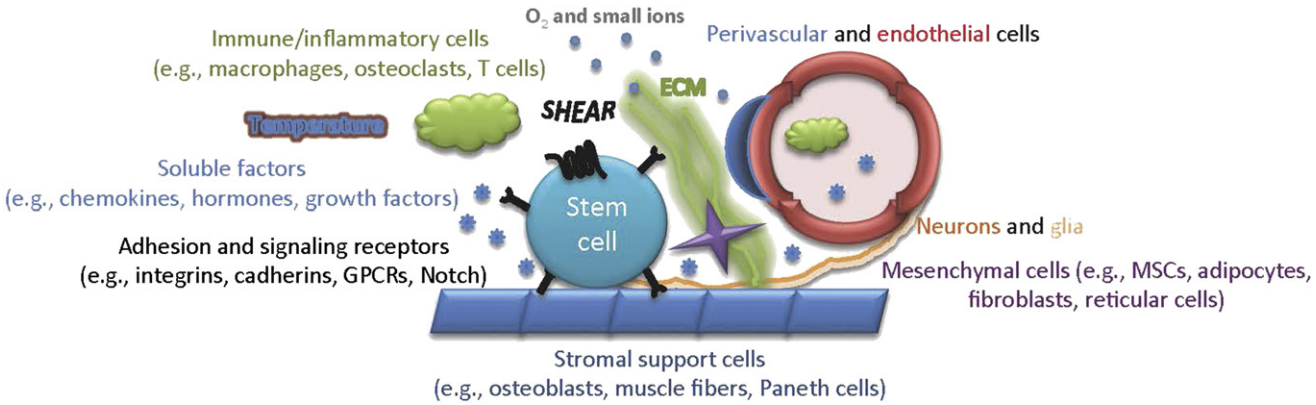

Figure 1. Constituents of a Stem Cell Niche
Stem cell niches are highly complex and dynamic, including both cellular and acellular components. This schematic depicts many of the critical constituents of stem cell niches, drawing predominantly from data in the hematopoietic system, and also including data from the skeletal muscle and gut. Labels are color-coded to match objects in the diagram, and some examples are given where appropriate. Please see text for additional detail. ECM, extracellular matrix; GPCRs, G protein-coupled receptors; MSC, mesenchymal stem cell.

(Chow et al., 2011; Christopher et al., 2011; Ehninger and Trumpp, 2011). Finally, temperature, shear forces, and chemical signals provided by the niche also influence stem cell behavior in response to the external environment (Adams et al., 2006; North et al., 2009; Wang and Wagers, 2011). Importantly, while the specific components that constitute a particular stem cell niche may vary in different tissues and under distinct physiological contexts, in all cases the signals provided by these cellular and acellular components appear to be integrated by stem cells to inform their fate decisions, including choices between quiescence or proliferation, self-renewal or differentiation, migration or retention, and cell death or survival.

The pivotal role of the niche in determining stem cell functions presents a powerful opportunity to manipulate stem cells to enhance their therapeutic efficacy. Indeed, because the niche, by definition, impacts stem cell function extrinsically, it may be argued that this anatomical structure represents an even more "druggable" target for regenerative medicine than the stem cell itself. Such "niche therapies" could be applied to enhance stem cell functionality—in transplantation, through endogenous targeting, or via in vitro model systems (Figure 2). The following paragraphs consider the progress, challenges, and opportunities for such approaches and how understanding the stem cell niche may ultimately enable full realization of the promise each presents.

Targeting the Niche to Enhance Stem Cell Transplant for Regenerative Medicine

One of the most celebrated successes in the use of stem cells for regenerative medicine has been the clinical implementation of bone marrow transplantation for regeneration of the blood-forming system (Thomas, 2000). The process of bone marrow transplant typically involves the harvesting of donor cells containing hematopoietic stem cells (HSCs) from either the marrow cavity or peripheral blood (after treatment with appropriate "mobilizing" agents that induce the migration of HSCs from the marrow into circulation), and infusion of those cells into a recipient whose own blood-forming cells have been impaired or ablated by chemotherapy or radiation. Thus, a primary challenge in bone marrow transplant (and likely in other tissue-specific transplant approaches that may be pursued in future studies) is achieving sufficient regeneration in a short enough period of time to be effective. In the case of the blood system, this requires (1) collection of sufficient numbers of stem cells for transplant, (2) efficient migration of these cells after intravenous injection to their proper locations within the bone marrow, and (3) proliferation of these cells in the body to rapidly replenish lost cells. Ineffectiveness or inefficiency at any of these steps can result in life-threatening graft failure. Therefore, strategies that can boost the rate or extent of regeneration, either by providing more regenerative cells or by increasing the per cell output of each stem cell transferred, may significantly reduce transplant-associated risk and increase the rate of successful engraftment. Importantly, strategies that target the stem cell niche could aid in both approaches. Indeed, targeting of the stem cell niche is already effectively employed in the clinical practice of marrow transplantation, wherein donors are treated with stem cell mobilizing agents, such as granulocyte-colony stimulating factor (G-CSF) or AMD3100. These agents activate niche remodeling and disrupt the normal interactions of HSCs with the marrow environment (Broxmeyer et al., 2005; Kollet et al., 2006; Méndez-Ferrer et al., 2010), thereby causing the egress of stem cells into the peripheral circulation where they can be easily collected for subsequent transplantation. Likewise, administration of lineage-specific hematopoietic cytokines, including granulocyte-macrophage-colony stimulating factor (GM-CSF) or erythropoietin, is routinely employed to support the enhanced production of particular blood cell lineages in patients with deficiencies in leukocytes or leukocyte subsets.

In addition to targeting the niche through mobilizing and differentiation agents, much interest has focused on strategies that may recapitulate a stem cell expanding niche ex vivo. Such approaches, if successful, could in theory generate increased numbers of cells for transplant. Although such ex vivo expansion approaches have been pursued for many decades, unfortunately for the most part without significant gains (Dahlberg et al., 2011),

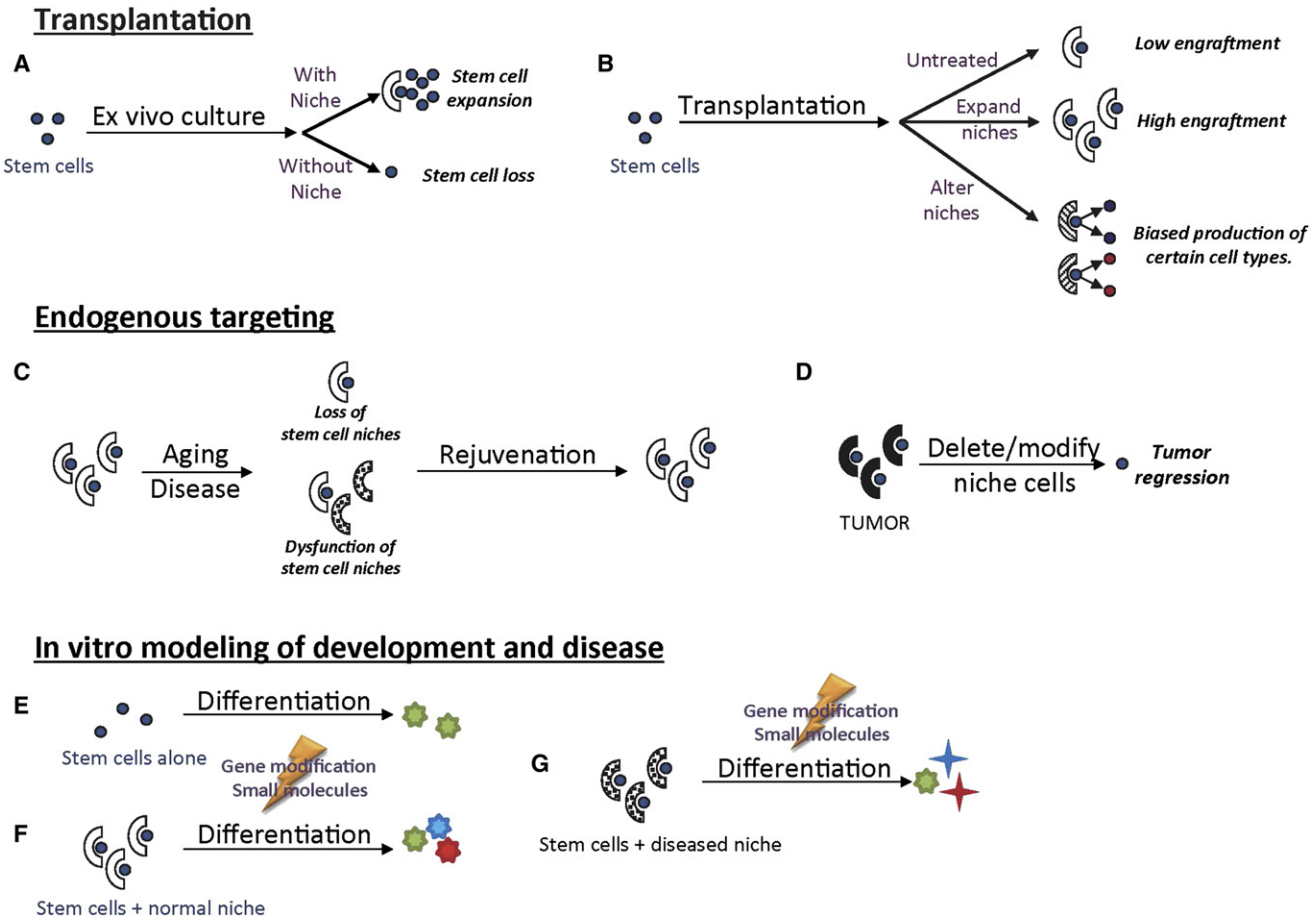

Figure 2. Potential Entry Points for Niche-Directed Stem Cell Therapies

Targeting the stem cell niche could have therapeutic value in a number of strategies aimed at using or manipulating stem cells for regenerative medicine. In the context of transplantation, ex vivo recapitulation of niche-derived signals could be used to expand stem cells for subsequent transplant (A), or to expand or alter the niches that are available in vivo in transplant recipients (B). Direct targeting of niche cells in vivo also could be used to replenish lost niches or reverse niche dysfunction (C), thereby restoring or enhancing endogenous regenerative potential. Conversely, modified, tumor-supportive niches could be targeted for deletion or modification to counteract their growth and metastasis-promoting activities (D). Finally, reconstitution of stem cell niches ex vivo has the potential to provide necessary extrinsic cues, which are lacking in cultures containing stem cells alone (E), to initiate in culture normal processes of development (F) that typically are inaccessible to experimental interrogation, and to uncover how these processes may be perturbed in disease to impede or pervert normal stem cell differentiation (G). Intervention in any of these culture systems with gene modification or small molecule supplementation could also provide novel systems for drug discovery.

recent advances in our understanding of the substantial complexity of the stem cell niche coupled with improved technologies for high-throughput screening and biomaterials fabrication are likely to reinvigorate this area of investigation (Peerani and Zandstra, 2010). Previous studies have reported successful expansion of clinically relevant numbers of hematopoietic stem and progenitor cells through endogenous (Varnum-Finney et al., 2000) or ligand-mediated (Varnum-Finney et al., 2003) activation of Notch signaling (a conserved cell-cell communication pathway that regulates cell fate and differentiation events in many different metazoan tissues; Liu et al., 2010). More recently, work using microfabricated arrays of stem cell regulatory factors (i.e., Wnt, Notch, and BMP2) together with ECM components demonstrated a complex interplay between matrix proteins and growth factors in the regulation of self-renewal and differentiation of neural stem cells (Soen et al., 2006). Moreover, studies of skeletal muscle stem cells have provided compelling data indicating that even relatively simplistic interventions, such as modulation of substrate elasticity, can profoundly impact the ex vivo expansion of regenerative cells, enabling significant tissue engraftment to be obtained from as few as 10 cultured precursor cells (Gilbert et al., 2010). Such modulation of matrix rigidity also has been used to bias the differentiation potential of mesenchymal stromal cells (MSCs), with stiffer matrices favoring osteogenic lineages (Engler et al., 2006). It is likely that similar principles, when applied to hematopoietic or other tissue stem cell systems, may have equivalently useful outcomes for stem cell expansion and cell fate modulation. Likewise, high throughput chemical screening using purified human HSCs has identified soluble signals, such as inhibition of ligand-induced signaling by the aryl hydrocarbon receptor (AhR), that can promote in vitro expansion of umbilical cord and mobilized peripheral blood-derived human HSCs (Boitano et al., 2010; M. Cooke, personal communication). Such unbiased screens likely illuminate natural mechanisms used by niche cells in vivo to modulate stem cell expansion, and thus, future studies of

this type could be further informed by direct analysis of endogenous niche signals to prioritize candidate pathways.

Niche-directed interventions also might be employed to boost support for transplanted stem cells after transplantation. In this regard, compelling preclinical data in mice suggest that activation of osteolineage cells by parathyroid hormone (PTH), which promotes the proliferation of nestin+ mesenchymal cells and encourages osteolineage differentiation (Calvi et al., 2003; Méndez-Ferrer et al., 2010), speeds posttransplant recovery of peripheral mature cells, improves pharmacological mobilization of HSCs, and protects mice from otherwise lethal hematoablative chemotherapy (Adams et al., 2007). Such studies supported the initiation of clinical trials to test the impact of PTH supplementation on donor cell mobilization and engraftment during sequential cord blood transplantation (ClinicalTrials.gov Identifier numbers: NCT00393380 and NCT00299780). Although the engraftment study was stopped early when toxicity endpoints (thought to be transplant-related, rather than drug-induced) were met, outcomes from the mobilization trial indicated that about half of patients who had failed a previous round of mobilization mobilized successfully after PTH (D. Scadden, personal communication). In a similar approach, treatment of irradiated mice with the peroxisome proliferator-activated receptor-gamma (PPAR-γ) inhibitor bisphenol A diglycidyl ether accelerated hematopoietic engraftment, apparently via inhibition of marrow adipogenesis (Naveiras et al., 2009). Such interventions, which target mesenchymal cell types that are components of the HSC niche in the bone marrow, may be particularly relevant for improving transplantation outcomes in aged individuals, who typically exhibit reduced bone density and increased adiposity. These age-related microenvironmental alterations could impair HSC function, and so, reversal of these changes might be predicted to enhance therapeutic engraftment in aged individuals (see below).

Targeting Endogenous Niches to Promote Regenerative Activity or Impede Deregulated Growth

In many acute and degenerative diseases, alterations in the stem cell niche may activate stem cell suppressive mechanisms that impair tissue regenerative potential (for review, see Jones and Rando, 2011; Liu and Rando, 2011; Rossi et al., 2008). This phenomenon is particularly evident in the context of physiological aging, where a number of tissues exhibit profound alterations in stem cell number and activity that coincide with reduced tissue function and a delay or failure to repair after injury. In the blood system, HSC numbers increase with age but HSC function declines (Morrison et al., 1996; Rossi et al., 2005), leading to impaired stem cell engraftment potential and skewed production of mature cell lineages by individual aged HSCs (Dykstra et al., 2011). Stem cell function is similarly impaired in the aged central nervous system (CNS), which exhibits reduced neurogenesis at baseline (Molofsky et al., 2006) and impaired remyelination activity after injury (Sim et al., 2002), and in the skeletal muscle, where deficiencies in satellite cell number and activation impede rapid repair of acutely damaged muscle fibers (Brack et al., 2005; Collins et al., 2007; Conboy et al., 2003, 2005). This inexorable decline in stem cell function stimulated by advancing age likely contributes to the progression of chronic diseases, particularly diseases that can span several decades of life (such as multiple sclerosis and some adult-onset forms of muscular dystrophy) and are therefore impacted by age-related deficits in tissue stem cells, even if those deficits are unrelated to the disease-causing factors. In this regard, recent studies in parabiotic mice have implicated age-variant systemic factors, including soluble factors (Brack et al., 2007; Conboy et al., 2005; Villeda et al., 2011) and circulating hematopoietic cells (Ruckh et al., 2012), in modifying the stem cell niche to promote or reverse the effects of aging on stem and progenitor cell function. Such studies highlight the dynamic nature of the stem cell niche, and the potential for endocrine, as well as paracrine, control of tissue regenerative function. These studies also point to discrete molecular entities, including inactivated Notch signaling (Conboy et al., 2005) or hyperactivated Wnt (Brack et al., 2007) or TGF-β (Carlson et al., 2008) signaling in skeletal muscle, and excessive levels of CCL11/eotaxin (Villeda et al., 2011) or ineffective activity of recruited phagocytes (Ruckh et al., 2012) in the CNS, as niche-derived targets for therapeutic intervention. Thus, niche-directed strategies that revert the stem cell microenvironment to a more "youthful" state may be effective in reversing age-associated stem cell defects and thereby restore robust regenerative potential to aging tissues.

Interestingly, even young animals may experience remodeling of stem cell niches that impacts tissue regenerative potential, particularly if they are exposed to prolonged metabolic perturbations. Obese, insulin-resistant, and diabetic individuals exhibit profound impairments in tissue repair, including ineffective healing of cutaneous wounds (Rafehi et al., 2011), poor regeneration of injured skeletal muscle (Hu et al., 2010), and aberrant regulation of immune and inflammatory cells (Mathis and Shoelson, 2011). As in aged animals, regenerative defects in the diabetic state appear to be modulated at least in part by blood-borne factors. Parabiotic experiments in a diabetic skin wounding model, where diabetic animals (which normally show impaired healing after skin wounding) were exposed to circulating factors found in normoglycemic animals, showed an accelerated rate of wound closure, enhanced angiogenesis, and an increased recruitment of inflammatory cells thought to be important in "clean-up" of the wound site in diabetic mice following parabiosis (Pietramaggiori et al., 2009). Likewise, recent data in the hematopoietic system reported a significant impairment of HSC mobilization in diabetic mice and patients (Ferraro et al., 2011). Given that impaired angiogenesis and altered inflammatory responses in many tissues are common manifestations of advancing age and diabetes, it is possible that these may represent common mechanisms by which modifications in the stem cell niche can suppress tissue regenerative function. Thus, niche-based therapeutics that prevent or reverse these alterations may be of broad benefit to the already large and ever-increasing population of individuals diagnosed with diabetes or metabolic syndrome.

In addition to aging and diabetes, endogenous targeting of the stem cell niche may also be desirable in situations of deregulated cell growth leading to cancer. Several intriguing studies support the existence of a specialized tumor microenvironment that plays a particular role in encouraging tumor cell growth and may promote the metastatic spread of malignant cancer stem cells (reviewed in Raaijmakers, 2011; Sneddon and Werb,

2007; Voog and Jones, 2010; Wels et al., 2008). Stromal cells isolated from established tumors often exhibit alterations in their gene expression profiles, including deregulation of secreted factors that may promote cell growth or inhibit normal differentiation. For example, stromal cells associated with human basal cell carcinomas (BCCs) show enhanced expression of antagonists of the bone morphogenetic protein (BMP) pathway, including Gremlin1 and Follistatin, when compared to normal stroma, and ex vivo supplementation of cultures of BBC cells with Gremlin1 inhibited BMP-stimulated tumor cell proliferation (Sneddon et al., 2006). Similarly, the dependence of a number of solid tumors, including pancreatic adenocarcinoma and colon carcinoma, on activated Hedgehog (Hh) signaling has been traced to a requirement for this pathway in the tumor mesenchyme, rather than in tumor cells themselves (Yauch et al., 2008). In one particularly striking example of a ''tumorigenic niche,'' conditional inactivation of the small RNA processing enzyme Dicer specifically in mouse osteolineage cells induced a modified niche that promoted myelodysplasia, leading ultimately to the emergence of an acute myelogenous leukemia that was independent of Dicer deletion in the hematopoietic compartment (Raaijmakers et al., 2010). These data indicate that gene disruption or deregulation in the niche can provide a ''fertile soil'' for the growth of malignant clones, and may underlie the emergence of some hematopoietic dysplasias. Targeting such aberrant niches, particularly in the early stages of disease, may be an effective strategy for reversing disease course (Figure 2), a notion supported by the observation that transplantation of dysplastic cells from the Dicer-deficient microenvironment to a wild-type host failed to transfer disease (Raaijmakers et al., 2010).

In a contrasting approach, recent studies suggest that targeting the niche to drive stem cell proliferation, rather than to inhibit it, may also hold clinical utility. In particular, it has been suggested that by altering the inflammatory tone of the stem cell niche, via modulation of cytokines such as interferon-alpha (IFN-α) and G-CSF, one might drive ''dormant'' HSCs or resting leukemic stem cells into cycle and thereby enhance the efficiency of chemotherapeutic ablation of tumor cells or of endogenous stem cells (which would likely enhance subsequent donor cell engraftment) (Essers and Trumpp, 2010). Such effects might also be accomplished by targeting nonmyelinating Schwann cells in the bone marrow, which appear to be responsible for maintaining HSC ''hibernation'' by activating latent TGF-β (Yamazaki et al., 2011).

Such niche-directed strategies may prove themselves to be equally relevant interventions in solid tumors as well. Studies in a mouse model of neurofibroma indicate that haploinsufficiency of the tumor suppressor *NF1* in the nonneural cells of the tumor microenvironment promotes tumor growth, in part by recruitment of dysfunctional mast cells that produce critical tumor growth factors (Yang et al., 2006; Zhu et al., 2002). Likewise, cancer-associated fibroblasts (CAFs) found in association with invasive breast cancers appear to support tumor initiation and progression, in part by elaboration of the chemokine CXCL12 (also known as stromal derived factor-1, SDF-1), which acts directly on breast cancer cells and also on endothelial progenitors to stimulate tumor angiogenesis (Orimo et al., 2005). Finally, modified niches may in some cases direct the formation of secondary tumors, producing factors that attract or retain metastatic cells at particular locations (Kaplan et al., 2006; Wels et al., 2008). In these situations, targeted strategies that ablate tumor-supportive niche cells, disrupt homing to these niches, or alter the ability of the niche to produce required growth factors or ''metastatic beacons'' may provide novel and effective strategies for inhibiting tumor cell growth and malignant progression (Jin et al., 2006; Lane et al., 2009; Raaijmakers, 2011).

Ex Vivo Models for Tissue Development and Disease: Opening the "Black Box" of Degenerative Disease

Human degenerative diseases vary widely in their etiology, pathology, and prognosis, and we know sadly little about the causes and early events in the vast majority of these afflictions. This knowledge gap relates in part to the fact that many degenerative diseases fail to manifest symptoms (and therefore generally lack diagnosis) until relatively late in the disease process, when many of the disease-initiating and tissue destructive events have already taken place. For example, in patients with type 1 diabetes, a degenerative pathology evoked by autoimmune destruction of pancreatic beta cells, diagnosis typically occurs only after the patient has lost 40%–90% of beta cell mass, depending on age (Gale, 2002; Klinke, 2008). Likewise, in Parkinson's disease, it has been estimated that pigmented neurons in the substantia nigra and striatal dopamine levels are decreased by up to 50 and 80%, respectively, before the symptomatic manifestation of their loss is detected (Fearnley and Lees, 1991; Marsden, 1990; Ross et al., 2004). Unfortunately, this complicated clinical situation forces a somewhat retrospective analysis of disease in human subjects, which generally is insufficient to reveal the fundamental underlying mechanisms that could be targeted early to prevent or reverse pathological expression of disease phenotypes. In this regard, patient-specific stem cells, which can undergo the same developmental processes that give rise to disease pathology in vivo, provide a unique opportunity to recapitulate disease processes in real time, under experimental scrutiny and subject to intentional manipulation, to discover exploitable vulnerabilities in the drivers of pathology. The groundbreaking development of induced reprogramming technology (Park et al., 2008a, 2008b; Takahashi et al., 2007; Takahashi and Yamanaka, 2006; Yu et al., 2007), and the resulting possibility of generating disease-specific induced pluripotent stem cells (iPSCs) from almost any human patient (Park et al., 2008a), has made this possibility a reality for many human disorders. Excitingly, studies that have characterized disease-specific phenotypes of patient iPSCs and evaluated the potential of these cells for drug discovery have for the most part supported the utility of this approach (Brennand et al., 2011; Kiskinis and Eggan, 2010; Liu et al., 2011; Zhang et al., 2011). Yet, at the same time, such studies reinforce the notion that highly reductionist approaches—which focus only on the cell type that is lost or damaged in a given disease—may overlook critical ''niche effects'' on disease progression. An illustrative case in point, motor neurons generated from mouse pluripotent stem cells expressing a mutant human gene associated with familial cases of amyotrophic lateral sclerosis (ALS, or ''Lou Gehrig's Disease,'' a lethal neurodegenerative disease caused by the death of motor neurons in the brain and spinal cord; Boillée et al., 2006) manifested a significantly greater

in vitro pathology when cultured together with glial cells that also carried the disease gene (Di Giorgio et al., 2007; Nagai et al., 2007). These data implicated toxic mediators produced by glial cells within the diseased neuronal niche as critical players in motor neuron loss and disease progression, and further studies using human pluripotent cell-derived motor neurons ultimately identified prostaglandin D2 (PGD2) signaling as a critical mediator of this toxic effect (Di Giorgio et al., 2008). Significantly, inhibition of the PGD2 receptor provided substantial protection to motor neurons cocultured with mutant glia, though this intervention had no effect on motor neurons cultured with wild-type glia (Di Giorgio et al., 2008). Thus, the discovery of this critical disease-promoting mechanism in ALS relied upon an in vitro system in which stem cells capable of producing the target cells of a disease were exposed to the disease-modified niche cells that signal their elimination.

Concluding Remarks

Stem cells hold tremendous potential for realizing the promise of regenerative medicine, but these cells are not solo actors in the drama of tissue maintenance and repair. As stem cells must respond rapidly and appropriately to a multitude of extrinsic signals, these cells are intricately connected with their surroundings and receive constant input from their niches, which direct their subsequent behavior. Through better understanding of the cellular players and molecular signals that constitute stem cell niches under different physiological and pathological conditions, we will develop more refined models of stem cell responses and may ultimately be able to dictate their activities to promote tissue regeneration. Likewise, by targeting dysfunctional or deregulated niches, we may design new strategies to combat stem cell loss, such as occurs in response to organismal aging and degenerative disease, and to prevent or reverse malignant transformation for the treatment of hematopoietic and non-hematopoietic tumors. Success in these endeavors will require a holistic view of stem cell regulation, exploiting new advances in in vivo stem cell analysis and ex vivo modeling to uncover novel entry points for niche-directed therapies.

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