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The HSC niche concept has turned 31 Has our knowledge matured?

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Abstract

The hematopoietic stem cell (HSC) niche is currently defined as the specific microenvironment in the bone marrow (BM) which anatomically harbors HSCs and governs their fate. It plays a pivotal role in regulating the survival and self-renewal ability of HSCs, protecting them from exhaustion while preventing their excessive proliferation. Many different stromal cell types have been proposed as putative constituents of the niche, but their integrated function is still unrevealed. Mechanisms by which stem/progenitor cell behavior is regulated in the niche include cell-to-cell interaction and the production of growth factors, cytokines, and extracellular matrix proteins. The HSC niche is a dynamic entity reflecting and responding to the needs of the organism. An understanding of how the niche participates in the maintenance of tissue homeostasis and repair offers new opportunities for the development of novel therapeutic tools.

Keywords

HSC niche; stem cells; microenvironment; osteoblastic cells; perivascular cells; regeneration

Introduction

Hematopoietic stem cells (HSCs) are characterized by the dual ability to self-renew, thereby maintaining their numbers, and to differentiate into all the lineages of the blood and immune system, thereby replenishing short-lived mature cells. In adulthood, HSCs have varying proliferative rates, with some serving as a deeply quiescent reserve pool and others rapidly entering into cycle upon external stimuli. The crucial decision between self-renewal or differentiation and quiescence or proliferation is tightly balanced by the integration of intrinsic factors and extrinsic cues provided by the particular microenvironment in which they reside. Supporting cells and extracellular matrix form this specialized microenvironment, which is called the “niche.”

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Conflicts of interest

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The definition of the HSC niche as the highly organized microenvironment that controls HSC homeostasis was first proposed by Schofield more than 30 years ago.¹ Because of the complex anatomy of the bone and the difficulties in its histologic analysis, experimental evidence for the existence of the niche was first provided only later and in the simplified model of *Drosophila melanogaster*'s ovary.² This work has demonstrated the existence of a heterologous cell type—the niche cell—found in a specific location in close proximity to the stem cell. Elegant experiments in this invertebrate model as well as in the gonads of *Caenorhabditis elegans* have revealed several mechanisms by which stem cell niches control stem cell behavior. The germ stem cells reside at the distal end of a tapered structure, and the relationship between dividing stem and supporting cells has been shown to affect the difference between symmetric and asymmetric stem cell divisions. Secreted molecules from the surrounding cells regulate stem cell proliferation and differentiation, while adhesion between stem cells and supporting stromal cells or the extracellular matrix anchors stem cells within the niche, providing polarity cues. Thus, the stem cell niche provides structural support, trophic support, topographic information, and the appropriate physiological signals to regulate stem cell function. This work in invertebrate models has led to emphasis on defining similar cell-based niche components in mammalian tissues. Extensive research in the field followed and many independent studies identified osteoblastic cells as the participating HSC niche cells. Nevertheless, it soon became clear that more than other cellular components of the bone marrow and their extracellular secretion are responsible for sustaining the HSC niche, which is a dynamic entity under constant reconstruction.

Osteoblastic cells regulate HSC fate

Because of the presence of osteoblastic cells on the endosteal surface, it was hypothesized that they may influence hematopoiesis. Further, in classic studies examining where immature hematopoietic cells reside in relation to bone surface, Lord and colleagues demonstrated that primitive cells were more closely associated with the endosteum. These prompted a series of subsequent *in vitro* studies.³ It was noted that osteoblasts have the potential to produce a vast array of cytokines, important for the expansion of hematopoietic myeloid progenitors, including G-CSF, GM-CSF, interleukin (IL)-6, IL-1, and transforming growth factor- β (TGF- β).⁴ In early experiments co-transplantation of osteoblasts purified from murine long bones with Lin⁻ BM cells enhanced engraftment and hematopoietic reconstitution in lethally irradiated mice, whereas the generation of new osteoblast-derived ectopic bones resulted in an increase in the number of HSCs. Moreover, in early imaging studies examining the homing site (or destination) of labeled transplanted HSCs, the engraftment of the most primitive HSCs occurred near the endosteum. These data suggested that osteoblasts lining the endosteal surface of the trabecular bone could serve as the primary support for HSCs.

HSCs have been shown to respond to osteoblast-specific secreted proteins, such as the matrix glycoprotein osteopontin. Osteopontin-deficient mice had increased numbers of hematopoietic progenitors, and when treated with parathyroid hormone (PTH), they exhibited an accentuated increase in HSC numbers.⁵ This indicated that osteopontin normally acts to constrain their amount in the stem cell niche. In addition *in vitro* treatment with osteopontin suppressed the cell cycling of HSCs while a marked increase in bromodeoxyuridine (BrdU)

incorporation into HSCs was observed in osteopontin-deficient mice when compared to wild-type ones.⁶ Furthermore, osteoblasts produce molecules that modulate HSC function such as angiopoietin 1 (Ang1), which in early studies was shown to maintain HSCs in a quiescent state through Ang1/Tie2 signaling. Ang1 produced by osteoblasts interacts with the receptor Tie2-expressing HSCs and increased their *in vivo* long-term repopulating activity, while protecting the HSC compartment from 5-fluorouracil treatment.⁷ A more recent study identified thrombopoietin (TPO) as another mediator of the osteoblast-HSC interaction in the niche. HSCs expressing the TPO receptor Mpl are a quiescent population in the BM closely associated with the TPO-producing osteoblasts, while exogenous TPO administration increased the entry of HSCs into G0 prior to their proliferation. On the contrary, inhibition of the signaling reduced the number of quiescent HSCs, releasing them from the niche and allowing their replacement by transplanted HSCs without prior irradiation.⁸

Osteoblastic cells are also capable of regulating major signaling pathways involved in self-renewal and differentiation in other stem cells systems. Osteoblasts express the Notch ligand, Jagged 1, which is markedly upregulated with activation of the osteoblast by the parathyroid hormone. *In vivo*, it was shown that increased production of Jagged1 by osteoblasts through activation of parathyroid hormone 1 receptor (PTH1R) induced Notch signaling in HSCs and increased the pool of the stem cells.⁹ Another study, however, showed that conditional deletion of both Jagged1 and Notch1 from BM cells does not affect HSCs. These data suggest that Notch signaling may affect HSCs only under circumstances of physiologic challenge, or that other members of the Notch family participate when a single receptor or ligand is deleted. Wnt signaling is another morphogen with effects on multiple stem cells types. Wnt signaling directs the differentiation fate of primitive mesenchymal cells toward the osteoblastic lineage. In hematopoiesis Wnt signaling has a wide range of effects. To assess the physiologic role of Wnt signaling in the HSC niche, the pan-inhibition of canonical signaling Dickkopf (Dkk-1), was expressed by an osteoblast-specific promoter in transgenic animals. The HSCs exhibited decreased Wnt target activation, increased cell cycling, and a loss of serial transplant capability. Therefore, Wnts do appear to play a role in the HSC niche and stem cell properties. HSC homing and retention in the niche has also been shown to involve osteoblast-secreted molecules. It has been demonstrated that osteoblasts produce CXC-chemokine ligand 12 or stroma-derived factor 1 (CXCL12 or SDF-1) in the BM, which mediates the lodgement and the retention of HSC in the niche by interacting with its receptor CXCR4 expressed on HSC cell surface. Annexin II, which is expressed on both osteoblasts and HSCs, plays a critical role in HSC homing and maintenance in the niche serving as an adhesion molecule between the two cell populations. Finally, the cell-to-cell interaction between osteoblasts and HSC via homotypic N-cadherin junctions has been postulated as an important regulator of the HSC fate decision, but this topic remains controversial.

Involvement of osteoblastic cells in HSC regulation and maintenance *in vivo* was first reported by two groups using engineered mouse models. In the first study, a bone morphogenic protein (BMP) receptor IA (BMPRIA) conditional knockout mouse was used to show that an increase in the number of osteoblastic cells was correlated with an increase

in the number of HSCs.¹⁰ In the second study, the use of transgenic mice expressing a constitutively active PTH and PTH-related receptors (PPRs) under control of the osteoblast-specific 2.3kb fragment of the $\text{I}\alpha$ collagen gene promoter resulted in a simultaneous increase in the number of both osteoblastic cells and HSCs in the BM. Likewise, systemic intermittent treatment with PTH expanded HSCs *in vivo*, while the addition of PTH to stromal cultures *in vitro* increased the number of osteoblastic cells and their ability to support LTC-IC. Moreover, treatment of recipient mice with PTH after BM transplantation conferred a survival advantage compared to that of vehicle-treated mice.⁹ The observation that conditional ablation of osteoblastic cells via gancyclovir treatment of transgenic mice expressing herpes virus thymidine kinase under the $\text{I}\alpha$ collagen gene promoter led to depletion of myeloid, lymphoid, and erythroid progenitor cells, followed by a switch to extramedullary hematopoiesis in the spleen,¹¹ supported the initial two studies. However, not all studies have indicated a link between osteoblastic cells and HSCs. Lymperi and colleagues noted that strontium induces increases in osteoblasts that did not alter HSCs,¹² and Kiel *et al.* showed that biglycan-deficient mice, in whom osteoblasts are reduced, had no change in HSCs.¹³ It may be that subsets of osteoblastic cells participate in HSC regulation and others do not.

Other components of the niche

Osteoblastic cells are a heterogeneous population thought to derive from multipotent mesenchymal progenitors. The specific role of each subset of osteoblastic cells in the niche remains to be assigned. In this context, other cell types derived from mesenchymal progenitors, such as the adipocytes, have emerged as regulators of the HSC. In one study it has been demonstrated that adiponectin, an adipocyte-secreted molecule, increases proliferation of HSCs, while maintaining their immature state.¹⁴ On the other hand, a more recent study showed that the content of adipocytes in the marrow inversely correlates with the hematopoietic activity.¹⁵ The participation of osteoclasts in HSC homeostasis has been also suggested by a study of Kollet *et al.*, who demonstrated that upon activation, osteoclasts actively participate into the mobilization of hematopoietic progenitors in the circulation through the cathepsin K-mediated cleavage of CXCL12.¹⁶ Furthermore the osteoclastic bone resorption actively changes the Ca^{+2} concentration in the BM microenvironment, which has been previously implicated in HSC engraftment. HSCs deficient in the calcium sensing receptor were unable to engraft bone marrow.¹⁷

The role of vascular and perivascular tissue

The capacity of HSCs to self-renew and differentiate during fetal development, before the creation of BM cavities, indicates that other niches, which do not involve bone cells, can also regulate their fate. During embryonic development there is an intimate relationship between the hematopoietic and endothelial lineages, which appear to arise from a common embryonic precursor, the hemangioblast.¹⁸ Embryonic hematopoiesis is in part driven by nitric oxide-induced emergence of hematopoietic cells from the dorsal aorta. In addition, cell lines or purified primary endothelial cells derived from the yolk sac or the aorta–gonad–mesonephros promote the maintenance and the clonal expansion of adult HSC *in vitro*, whereas in adult life, HSCs are present in extramedullary tissues, such as the liver and the

spleen, where hematopoiesis occurs for a long time despite the absence of endosteum.¹⁹ Most HSCs mobilized to the adult spleen localize adjacent to sinusoids,²⁰ suggesting that HSCs in extramedullary tissues may reside within vascular niches. However, there are no data to directly show that perivascular cells in these tissues promote the maintenance of HSCs. Thus, the existence of extramedullary vascular niches, in the adult, remains to be truly defined.

Evidence indicating that BM vasculature can regulate hematopoiesis is clear for lineage-committed cells. Myeloid progenitors and particularly megakaryocytes associated with sinusoids are modulated by vascular growth factor production. For stem cells, the data are less clear. BM endothelial cells constitutively express cytokines, such as SDF-1, and adhesion molecules, such as endothelial-cell (E)-selectin and vascular cell-adhesion molecule 1 (VCAM1), which are important for HSC mobilization, homing, and engraftment.^{21,22} With the identification of the SLAM family antigens CD150, CD244, and CD48 as useful markers for defining HSCs, about 60% of BM HSCs were found adjacent to the fenestrated endothelium of BM sinusoids by immunohistochemical studies.²⁰ Conditional loss of gp130, the common cytokine receptor subunit, in endothelial cells resulted in a reduction in BM cellularity, but not a loss of HSCs.²³ Therefore we still lack definitive proof of a regulatory role for vascular and perivascular cells in HSC persistence. Thus it is not yet clear that such cells can be formally considered part of the HSC niche, although they clearly participate in HSC localization.

A recent study demonstrated that CD146-expressing human mesenchymal progenitors found perivascularly in bone marrow were uniquely capable of forming a hematopoietic microenvironment to heterotopic sites upon transplantation. These cells expressed factors that regulate HSC maintenance, such as Ang1 and CXCL12, suggesting that they might have a dynamic role in creating endogenous niches.²⁴ However, it must be noted that it is still unclear whether perivascular cells indeed promote the maintenance of HSCs or whether HSCs are localized around the sinusoids prior to their migration elsewhere. Nevertheless, recent evidence from our lab has demonstrated that the previously proposed dichotomy between osteoblastic and perivascular niches is not anatomically feasible at least in the calvarium.²⁵

HSCs out of their niches

To make the situation even more complex, HSCs are not static. Even though the majority of HSCs remain confined to the BM cavity, protected in their niches, a small proportion constantly circulates in the peripheral blood. The first experimental proof for the concept of circulating stem cells came from studies in mice demonstrating that transplantation of whole blood could reconstitute hematopoiesis in lethally irradiated recipients.²⁶ Extensive research in the 1980s and '90s investigating the effect of cytokines and interleukins on hematopoiesis *in vitro* and *in vivo*, in combination with the clinical observations that hematopoietic progenitor numbers are changed in response to chemotherapy, suggested that the physiologic process of HSC egression from the BM can be pharmacologically modulated. The use of mobilizing regimens for the collection of HSCs from the peripheral blood of donors rather than from the BM soon became common clinical practice in transplantation

settings far before understanding the mechanisms underlying this phenomenon. The most efficient cytokine currently used in the clinic to mobilize HSCs is the granulocyte colony-stimulating factor (G-CSF) or its pegylated form used in single administration (Peg-G-CSF).

In early studies, it was demonstrated that mobilization with repeated stimulations of G-CSF triggered the activation of neutrophils that released serine proteases, such as the neutrophil elastase and cathepsin G. The neutrophil-secreted proteases in turn cleaved VCAM-1 on stroma cells, perturbing the $\alpha 4 \beta 1$ integrin-mediated anchorage of stem and progenitor cells to the BM microenvironment.²⁷ It was then shown that G-CSF-induced mobilization involved the modulation of the SDF-1/CXCR4 axis, whereby the reduction of the SDF-1 levels and the upregulation of its receptor CXCR4 were correlated with stem cell mobilization.²⁸ Previously, it had been shown that altering the SDF1/CXCR4 axis can induce mobilization of HSC.²⁹ The combination of the bicyclam molecule, AMD3100, which specifically and reversibly blocks SDF-1 binding to CXCR4, with the G-CSF has been recently successfully used in clinical trials to mobilize CD34 in patients who had previously failed mobilization with the standard regimens.³⁰

However, although evidence suggested that the mobilization effect of G-CSF lies in its capacity to modify the SDF1 gradient (CXCL12) between the bone marrow and the peripheral blood, favoring the release of HSCs, the exact mechanism by which this occurs has not been completely clarified. Only recently have a number of studies reported that G-CSF can act indirectly through the modulation of the microenvironment by increasing the level of noradrenaline (NA). NA bonds to beta-3 adrenergic receptors expressed on niche cells, leading to a rapid suppression of their function and to a consequent reduction in the synthesis of CXCL12 (SDF1).³¹ The chemokine gradient therefore becomes permissive for the migration of HSCs to the bloodstream. The same group of authors has shown that the release of HSCs into the peripheral blood by the sympathetic nervous system (SNS) through noradrenergic stimulation is governed by a physiologic circadian rhythm.³² The biological significance of the cyclical variation in HSC recirculation is to date unknown. However, it is extremely appealing to think that the SNS may function by integrating the information provided by various organs and tissues in normal and stress conditions (such as ischemia and organ damage), thus participating in the regulation of the function of the resident stem cells. CXCL12 has been proven to be expressed in skin, bile ducts, endothelial cells of the central nervous system (CNS), and in the heart.³³

The circadian oscillations of HSC release from the BM, apart from contributing to host defense or tissue repair, could also be a homeostatic mechanism for the maintenance of a fixed number of the most fit HSCs in the BM niches. The increase of HSC numbers in the peripheral blood during periods of light overlaps with higher bone-remodeling activity,³⁴ at least in mice. Considering that bone and BM function as an integrated system, whereby modifications to bone are also expected to modify the BM niches, one could speculate that it is the reconstruction of the niches that sends HSCs out of their home. In this view, the bone remodeling process constantly creates new niches that will be filled with the most potent HSCs selected by virtue of their capacity to successfully undergo trafficking and engraftment. Ecological niches are occupied with the best-fitted organism and like-wise HSC niches must be filled with the best-suited cells.

Cancer stem cell niche and therapeutic opportunities

This constant selective pressure, however, is a double-edged phenomenon: the temporarily vacant niches could be invaded by malignant cells, whereby they can proliferate, expressing their tumorigenic potential. It is known that leukemic cells can exploit the migratory pathways of normal cells to hijack the niche, possibly employing the same molecules that normal cells do to interact with their intimate microenvironment.³⁵

On the other hand, since it is the niche that tightly regulates the size of the HSC pool, it is feasible to hypothesize that perturbation of its function could enable outgrowth of abnormal, including malignant, stem cells. The existence of a cancer stem cell niche has been supported by the clinical observation of donor-derived leukemia in allogeneic transplantation. In these cases, the relapse of the disease is driven by donor cells that acquire the same immunophenotypical and molecular features as the recipient cancer cells.³⁶ In animal models it has been shown that by knocking out the retinoic acid gamma receptor, a myeloproliferative syndrome is developed that is not related to an intrinsic dysfunction of the HSCs.³⁷

These observations raise the question of whether the niche can be a target for therapeutic manipulation. In fact, experimental evidence has indicated that the use of the bone remodeling agent PTH protected resident HSCs from cytotoxic damage during exposure to chemotherapy and improved harvests of stem cells from treated animals and engraftment outcome,³⁸ paving the way for the ongoing clinical trials in humans that aim at improving stem cell transplantation therapy. Along similar lines, evidence that activation of HSCs by prostaglandin E2 and its downstream G α s pathway, thus altering HSC engraftment efficiency, has lead to active clinical trials,^{39,40} which indicates that HSC niche interaction can have clinical implications. Further unravelling the differential mechanisms that regulate the crosstalk between normal as opposed to cancer stem cell niche and HSCs may allow us to develop new pharmacologic tools to selectively target these altered pathways and restore their function.

References

1. Schofield R. The relationship between the spleen colony-forming cell and the haemopoietic stem cell. *Blood Cells*. 1978; 4:7–25. [PubMed: 747780]
2. Xie T, Spradling AC. Decapentaplegic is essential for the maintenance and division of germline stem cells in the *Drosophila* ovary. *Cell*. 1998; 94:251–260. [PubMed: 9695953]
3. Lord BI, Testa NG, Hendry JH. The relative spatial distributions of CFUs and CFUc in the normal mouse femur. *Blood*. 1975; 46:65–72. [PubMed: 1131427]
4. Taichman RS, Reilly MJ, Emerson SG. Human osteoblasts support human hematopoietic progenitor cells *in vitro* bone marrow cultures. *Blood*. 1996; 87:518–524. [PubMed: 8555473]
5. Stier S, et al. Osteopontin is a hematopoietic stem cell niche component that negatively regulates stem cell pool size. *J. Exp. Med*. 2005; 201:1781–1791. [PubMed: 15928197]
6. Nilsson SK, et al. Osteopontin, a key component of the hematopoietic stem cell niche and regulator of primitive hematopoietic progenitor cells. *Blood*. 2005; 106:1232–1239. [PubMed: 15845900]
7. Arai F, et al. Tie2/angiopoietin-1 signaling regulates hematopoietic stem cell quiescence in the bone marrow niche. *Cell*. 2004; 118:149–161. [PubMed: 15260986]
8. Yoshihara H, et al. Thrombopoietin/MPL signaling regulates hematopoietic stem cell quiescence and interaction with the osteoblastic niche. *Cell Stem Cell*. 2007; 1:685–697. [PubMed: 18371409]

9. Calvi LM, et al. Osteoblastic cells regulate the haematopoietic stem cell niche. *Nature*. 2003; 425:841–846. [PubMed: 14574413]
10. Zhang J, et al. Identification of the haematopoietic stem cell niche and control of the niche size. *Nature*. 2003; 425:836–841. [PubMed: 14574412]
11. Visnjic D, et al. Hematopoiesis is severely altered in mice with an induced osteoblast deficiency. *Blood*. 2004; 103:3258–3264. [PubMed: 14726388]
12. Lymperi S, et al. Strontium can increase some osteoblasts without increasing hematopoietic stem cells. *Blood*. 2008; 111:1173–1181. [PubMed: 17971481]
13. Kiel MJ, Radice GL, Morrison SJ. Lack of evidence that hematopoietic stem cells depend on N-cadherin-mediated adhesion to osteoblasts for their maintenance. *Cell Stem Cell*. 2007; 1:204–217. [PubMed: 18371351]
14. DiMascio L, et al. Identification of adiponectin as a novel hemopoietic stemcell growth factor. *J. Immunol*. 2007; 178:3511–3520. [PubMed: 17339446]
15. Naveiras O, et al. Bone-marrow adipocytes as negative regulators of the haematopoietic microenvironment. *Nature*. 2009; 460:259–263. [PubMed: 19516257]
16. Kollet O, et al. Osteoclasts degrade endosteal components and promote mobilization of hematopoietic progenitor cells. *Nat. Med*. 2006; 12:657–664. [PubMed: 16715089]
17. Adams GB, et al. Stem cell engraftment at the endosteal niche is specified by the calcium-sensing receptor. *Nature*. 2006; 439:599–603. [PubMed: 16382241]
18. Kennedy M, et al. A common precursor for primitive erythropoiesis and definitive haematopoiesis. *Nature*. 1997; 386:488–493. [PubMed: 9087406]
19. Taniguchi H, et al. Presence of hematopoietic stem cells in the adult liver. *Nat. Med*. 1996; 2:198–203. [PubMed: 8574965]
20. Kiel MJ, et al. SLAM family receptors distinguish hematopoietic stem and progenitor cells and reveal endothelial niches for stem cells. *Cell*. 2005; 121:1109–1121. [PubMed: 15989959]
21. Sipkins DA, et al. *In vivo* imaging of specialized bone marrow endothelial microdomains for tumour engraftment. *Nature*. 2005; 435:969–973. [PubMed: 15959517]
22. Avecilla ST, et al. Chemokine-mediated interaction of hematopoietic progenitors with the bone marrow vascular niche is required for thrombopoiesis. *Nat.Med*. 2004; 10:64–71. [PubMed: 14702636]
23. Yao L, et al. Bone marrow dysfunction in mice lacking the cytokine receptor gp130 in endothelial cells. *Blood*. 2005; 106:4093–4101. [PubMed: 16118327]
24. Sacchetti B, et al. Self-renewing osteoprogenitors in bone marrow sinusoids can organize a hematopoietic microenvironment. *Cell*. 2007; 131:324–336. [PubMed: 17956733]
25. Lo Celso C, et al. Live-animal tracking of individual haematopoietic stem/progenitor cells in their niche. *Nature*. 2009; 457:92–96. [PubMed: 19052546]
26. Goodman JW, Hodgson GS. Evidence for stem cells in the peripheral blood of mice. *Blood*. 1962; 19:702–714. [PubMed: 13900318]
27. Levesque J, et al. Vascular cell adhesion molecule-1 (CD106) is cleaved by neutrophil proteases in the bone marrow following hematopoietic progenitor cell mobilization by granulocyte colony-stimulating factor. *Blood*. 2001; 98:1289–1297. [PubMed: 11520773]
28. Petit I, et al. G-CSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4. *Nat. Immunol*. 2002; 3:687–694. [PubMed: 12068293]
29. Shen H, et al. CXCR4 desensitization is associated with tissue localization of hemopoietic prgenitor cells. *J. Immunol*. 2001; 166:5027–5033. [PubMed: 11290783]
30. Calandra G, et al. AMD3100 plus G-CSF can successfully mobilize CD34+ cells from non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma patients previously failing mobilization with chemotherapy and/or cytokine treatment: compassionate use data. *Bone Marrow Transplant*. 2008; 41:331–338. [PubMed: 17994119]
31. Katayama Y, et al. Signals from the sympathetic nervous system regulate hematopoietic stem cell egress from bone marrow. *Cell*. 2006; 124:407–421. [PubMed: 16439213]
32. Mendez-Ferrer S, et al. Haematopoietic stem cell release is regulated by circadian oscillations. *Nature*. 2008; 452:442–447. [PubMed: 18256599]

33. Askari AT, et al. Effect of stromal-cell-derived factor 1 on stem-cell homing and tissue regeneration in ischaemic cardiomyopathy. *Lancet*. 2003; 362:697–703. [PubMed: 12957092]
34. Simmons DJ, Nichols G Jr. Diurnal periodicity in the metabolic activity of bone tissue. *Am. J. Physiol*. 1966; 210:411–418. [PubMed: 5901786]
35. Bendall LJ, Kortlepel K, Gottlieb DJ. Human acute myeloid leukemia cells bind to bone marrow stroma via a combination of beta-1 and beta-2 integrin mechanisms. *Blood*. 1993; 82:3125–3132. [PubMed: 7693037]
36. Flynn CM, Kaufman DS. Donor cell leukemia: insight into cancer stem cells and the stem cell niche. *Blood*. 2007; 109:2688–2692. [PubMed: 17132724]
37. Walkley CR, et al. A microenvironment-induced myeloproliferative syndrome caused by retinoic acid receptor gamma deficiency. *Cell*. 2007; 129:1097–1110. [PubMed: 17574023]
38. Adams GB, et al. Therapeutic targeting of a stem cell niche. *Nat. Biotechnol*. 2007; 25:238–243. [PubMed: 17237769]
39. Adams GB, et al. Haematopoietic stem cells depend on Galpha(s)-mediated signalling to engraft bone marrow. *Nature*. 2009; 459:103–107. [PubMed: 19322176]
40. Hoggatt J, et al. Prostaglandin E2 enhances hematopoietic stem cell homing, survival, and proliferation. *Blood*. 2009; 113:5444–5455. [PubMed: 19324903]