

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Hematopoietic Stem Cell Niche: Role in Normal and Malignant Hematopoiesis

Sergio P. Bydlowski, Debora Levy,
Jorge M.L. Ruiz and Juliana Pereira

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/55508>

1. Introduction

A stem-cell niche can be defined as a spatial structure in which stem cells are housed and maintained by allowing self-renewal in the absence of differentiation. The concept of the stem-cell niche was initially proposed in invertebrates where they were first characterized; the control of germ line stem cell maintenance and differentiation was observed in ovarian and testicular *D. melanogaster* niches (Wilson & Trumpp, 2006).

Hematological stem cells (HSCs) can be initially identified in the developing embryo in aorta-gonada-mesonephro regions, from where they migrate into the fetal liver and subsequently move into the bone marrow (BM) after birth. During development, HSCs undergo active self-renewal to expand the pool size, but then become largely quiescent and stay in a steady state in adult BM, where their maintenance is tightly regulated (Oh & Kwon, 2010).

The link between bone-marrow formation (hematopoiesis) and bone development (osteogenesis) was first recognized in the 1970s. It was noted that whilst HSCs in the bone marrow drive hematopoiesis during the whole life of organisms, when they are removed from the bone marrow, they lose the ability to self-renewal, indicating similar dependence of HSCs on extrinsic signals (Lilly *et al.*, 2011). The term 'niche' used for the specific HSC bone-marrow microenvironment was first coined by Schofield (1978), who observed that HSC growth was not supported in the spleen in the same manner as in the bone marrow; he also proposed that HSCs are in intimate contact with bone, and that cell-cell contact was responsible for the apparently unlimited proliferative capacity and inhibition of maturation of HSCs.

This concept has since been further developed, and it is now widely accepted that specific anatomical regions within the bone marrow comprise specialized niches for HSC development

and normal blood cell production (Noll *et al.*, 2012). The niche is composed of a vast milieu of cellular and humoral factors.

The advancement of our understanding of the interactions between bone, the microenvironment and hematopoiesis is rapidly accelerating. Research continues on the identification and characterization of individual cell populations constituting the hematopoietic stem cell (HSC) niche. Whether there are one or multiple HSC niches and how cells within the HSC niche interact with each other are also subjects of interest (Shen *et al.*, 2012).

Recently it has been suggested that two main microenvironments form the bone marrow niches: 1. the endosteal niche, where osteoblasts derived from mesenchymal precursors are localized in the endosteal regions, and 2. The vascular niche, which might be involved in HSC maintenance within the bone marrow (Chotinantakul *et al.*, 2012).

2. The endosteal niche

The first direct evidence for cells having stem cell-supporting activity in bone formation was provided by studies in which both mouse and human osteoblast cell lines were shown to secrete a large number of cytokines that promote the proliferation of hematopoietic cells in culture (Wilson & Trumpp, 2006). Studies in the 1970s indicated that undifferentiated hematopoietic cells are localized close to the endosteal bone surface, and that differentiated cells move toward the central axis of the marrow. The endosteum is the interface between bone and bone marrow and constitutes a reservoir of HSCs that can be mobilized, restoring hematopoiesis in response to tissue injury. Although bone is a hard and stiff organ, the endosteal niche is not so; it rather presents plasticity and is under self and systemic regulation.

After the identification of niches in the endosteal region, cells in the endothelial lining were proposed as a cellular component of the niche. However, heterogeneous cell populations were found in endosteal regions that included mature bone lining cells, osteoblasts, and preosteoblasts (Oh *et al.*, 2010).

2.1. Osteoblastic cells

Osteoblasts are responsible for the production of matrix, which they secrete at the site of the bone, as well as for bone mineralization. Eventually, osteoblasts either get surrounded by matrix and end up as osteocytes or they become bone-lining cells, which is a reversible process (ter Rurne *et al.*, 2010). The bone-forming osteoblastic cells are crucial players for the homeostasis of the hematopoietic tissue with its high turnover. In 1994, primary human osteoblasts were shown to stimulate the proliferation of primitive CD34+ hematopoietic progenitors *in vitro*, which raised the possibility that osteoblasts are involved in hematopoiesis (Nagasawa *et al.*, 2011).

Involvement of osteoblastic cells in HSC regulation and maintenance *in vivo* was first reported by two groups using engineered mouse models (Lymperi *et al.*, 2010). 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.

HSCs proliferation and differentiation is regulated by a wide variety of cytokines, growth factors, and other signaling molecules. Osteoblastic cells synthesize a number of cell-signaling molecules that appear to contribute to the maintenance and regulation of HSCs by the endosteal niche such as (table1):

- Jagged, a ligand for Notch receptors expressed on HSCs which is markedly upregulated with activation of the osteoblast by the parathyroid hormone. Activation of Notch receptors on HSCs has been shown to inhibit differentiation and enhance their self renewal capacity *in vitro* (Butler *et al.*, 2011). Notch signalling is important *in vivo* for controlling HSC self renewal and differentiation during hematopoietic stress conditions (Lilly *et al.*, 2011).
- Thrombopoietin (THPO) and angiopoietin (Ang-1), which bind to cell surface receptors MPL and Tie2, respectively, are expressed on HSCs. These cytokines are thought to be important as THPO and Ang-1 knockout mice have decreased numbers or defects in bone marrow HSCs. The interaction of Ang-1 with its Tie2 receptor activates β 1-integrin and N-cadherin, enhances quiescence, and maintains the long term repopulating ability of HSCs; it also protects against apoptosis by activating the PI3K pathway (Lilly *et al.*, 2011)
- Osteopontin, a matrix glycoprotein expressed by the osteoblasts supports the adhesion of HSC to the osteoblastic niche and negatively regulates HSC proliferation, contributing to the maintenance of a quiescent state (Guerrouahen *et al.*, 2011).
- The chemokines and their receptors can control HSC behaviour The best understood chemokine, in this regards, is the stromal-derived factor-1 (SDF-1), also called chemokine C-X-C motif ligand 12 (CXCL12). The SDF-1 receptor is the C-X-C chemokine receptor type 4 (CXCR4) and is expressed on HSCs and progenitors (Lilly *et al.*, 2011). SDF-1 belongs to α -chemokines that functions as chemoattractant for both committed and primitive hematopoietic progenitors and regulates embryonic development including organ homeostasis (Ratajczak *et al.*, 2006). SDF-1 counteracts with its cognate receptor CXCR4, that is widely expressed in several tissues including hematopoietic and endothelial cells. SDF-1/CXCR4 signaling plays a critical role during embryonic development by regulating B-cell lymphopoiesis, myelopoiesis in bone marrow and heart ventricular septum formation. In addition, SDF-1 has been shown to mediate the recruitment of endothelial progenitor cells (EPCs) from the bone marrow through a CXCR4 dependent mechanism suggesting the functional role in vasculogenesis in which EPCs could form blood vessels (Chotinantakul & Leeanansaksiri, 2012).
- Both HSC and osteoblasts express N-cadherin, and bone marrow imaging studies suggest that spindle-shaped bone-lining osteoblasts (so-called SNO cells) communicate with HSC through N-cadherin interactions. BrdU incorporation studies demonstrated that quiescent HSCs with moderate N-cadherin reside close to osteoblasts which have high N-cadherin expression. Furthermore, upregulation of N-cadherin on osteoblasts increases adherence of HSC on the endosteal surface, which is associated with HSC quiescence and diminished differentiation (Coskun & Hirschi, 2010).

- Early HSC characterization studies led to the discovery of a growth factor secreted by osteoblasts, called stem cell factor (SCF) that regulates HSC activity *in vivo* and self-renewal *in vitro*. HSCs express a transmembrane receptor tyrosine kinase called stem cell factor receptor (C-Kit) that can bind to SCF, activating intracellular signaling important for HSC regulation (Audet *et al.*, 2002).
- Members of the Wntless (Wnt) family of lipid-modified proteins have been also investigated in hematopoiesis. The Frizzled (Fzd) receptors act as Wnt receptors which activate downstream signaling in the Ctnnb1-dependent canonical and non-canonical pathways. Several components of the Wnt signaling machinery have been shown to play a role in HSC self-renewal. Wnt signaling is important in bone formation and in enlargement of endosteal surfaces. Several lines of evidence suggest that Wnt signaling in endosteal stromal cells may affect HSC maintenance, not by intrinsic signals, but by signals originated from the stromal cells. Wnt signaling may not be intrinsically involved in the maintenance of normal HSC during hemostasis or self-renewal. However, there are data suggesting that changes of Wnt signaling in endosteal stromal cells affect HSC maintenance through extrinsic mechanisms (Renstrom *et al.*, 2010).

Molecule	Function
Jagged (Notch receptor)	Control HSC self-renewal and differentiation during hematopoietic stress conditions
Thrombopoietin and angiopoietin	Maintenance of HSC in the niche in quiescence state with a link to cell-cycle control
Osteopontin	Maintenance of a quiescent state
SDF-1 (or CXCL12)	Expressed in the stromal cells; attracts HSC
CXCR-4	Expressed in HSCs; receptor of SDF-1
N-cadherin	HSC quiescence and decrease in differentiation
SCF	Activation of intracellular signaling important for HSC regulation
Wnt	HSC self-renewal

Table 1. Molecules that regulate HSC activity

2.2. Endothelial cells

Endothelial cells were proposed to be important in the HSC microenvironment. *In vivo* and tissue section imaging studies localize HSCs next to endothelial cells. Also, endothelial cells secrete soluble factors that can expand human primitive hematopoietic cells *ex vivo*. However, endothelial cells have not yet been shown to be a necessary regulatory component of the HSC microenvironment *in vivo* (Frisch *et al.*, 2008).

2.3. Osteoclasts

These cells are formed by fusion of multiple granulocyte–macrophage progenitor cells, a process mediated by osteoblasts. It reabsorb the mineralized bone matrix formed by chondrocytes or osteoblasts and located in endosteal niches. The role of osteoclasts in hematopoiesis remains a controversial issue. It has been reported that osteoclasts degrade endosteal niche components and enhance mobilization of hematopoietic progenitor cells (Kollet *et al.*, 2006). Enzymes secreted by osteoclasts are responsible for the release of HSCs from the endosteal niche. These enzymes are able to cleave factors that promote the interaction between HSCs and their niche. On the other hand, results have been published that suggest that osteoclast activity can promote lodgment of HSCs at the endosteal niche (ter Huurner *et al.*, 2010). Further studies will be needed to clarify how osteoclasts regulate hematopoietic stem and progenitor cell behavior (Sugiyama & Nagasawa *et al.*, 2012).

3. Vascular niche

Hematopoiesis and vascularization occur concurrently during development. In fact, HSCs and endothelial cells are derived from the same progenitor cells (termed hemangioblasts) at the embryonic stage and are closely related to the ontogeny of hematopoiesis (Yin & Li, 2006). The presence of a second specialized HSC microenvironment in the bone marrow has recently been postulated, as a large proportion of CD150⁺ HSCs was observed to be attached to the fenestrated endothelium of bone marrow sinusoids (Wilson & Trumpp, 2006).

The vascular niche promotes proliferation and differentiation, active cycling, and short-term HSCs. Most purified HSCs, containing CD150⁺ CD48[−] CD41[−] Lin[−] cells, were found to be mainly associated with the sinusoidal endothelium lining blood vessels, suggesting that endothelial cells create a cellular niche for HSCs. Endothelial cells in the vascular niche environment contacting HSCs also provide maintenance signals on the HSC behavior (Can, 2008). However, it is essential to keep in mind that vasculature is not compartmentalized to the central region of bone marrow and, in fact, the endosteal region of bone is also vascularized. Therefore, the proposed osteoblast and vascular niches within marrow are not completely separable, and may function interdependently to generate and sustain HSCs (Coskun & Hirschi, 2010).

The vascular niche has been shown to produce factors important for mobilization, homing, and engraftment of HSC. Endothelial cells expressing vascular cell-adhesion molecule-1 (VCAM-1) associate closely with megakaryocytes and their progenitors through VLA-4 in response to chemotactic factors, stromal cell-derived factor-1 (SDF1) and fibroblast growth factor-4 (FGF4); thus, they provide a niche for megakaryocyte maturation and platelet production (Avecilla *et al.*, 2004).

Two perivascular cell groups that possess mesenchymal cell properties function as niche cells: 1. CXC chemokine ligand 12 (CXCL-12)-abundant reticular cells (CAR cells), and 2. Nestin 234⁺ mesenchymal stem cells (Nakamura-Ishizu & Suda, 2012).

3.1. CAR cells

In human bone marrow, such reticular cells constitute the subendothelial (adventitial) layer of sinusoidal walls projecting a reticular process that is in close contact with HSCs. Interestingly, these reticular cells were derived from a specific subset of mesenchymal cells (CD146^b) that had been shown to produce either reticular or endosteum of the ectopic hematopoietic microenvironment (HME), referred to as skeletal stem cells (Sugiyama & Nagasawa, 2012).

These cells have recently been shown to be high secretors of SDF-1 (CXCL12), and as a result they have been named CXCL12 abundant reticular (CAR) cells. Phenotypically they express VCAM-1, CD44, 238 platelet-derived growth factor receptor (PDGFR α and PDGFR β) and possess adipogenic and osteogenic differentiation capacity (Nakamura-Ishizu & Suda, 2012). Histochemical analysis revealed that all bone marrow sinusoidal endothelial cells are surrounded by a proportion of CAR cells, however, CAR cells do not express the pan-endothelial marker platelet/endothelial cell-adhesion molecule 1 (PECAM-1)/CD31 or the smooth muscle cell marker and smooth muscle α -actin (SM α A), suggesting that they are different from endothelial cells and smooth muscle cells (Sugiyama & Nagasawa, 2012).

The depletion of CAR cells using a diphtheria toxin mouse model reduces the cycling of lymphoid and erythroid progenitors, as well as the total HSC cell number and cell cycling, reflecting that CAR cells regulate the proliferation of HSC rather than its quiescence. Ablation of CAR cells did not influence other niche cell compartments such as endothelial cells or osteoblasts (Lilly *et al.*, 2011). However, results based on the short term duration of the CAR cell deletion underestimate the influence that CAR cells may convey on other niches.

3.2. NES+ cells

Nestin is an intermediate filament protein that was originally identified as a marker of neural progenitor. Its expression has subsequently been detected in a wide range of progenitor cells and endothelial cells (Sugiyama & Nagasawa, 2012). NES⁺ MSCs can be differentiated into adipocytes, osteoblasts and chondrocytes, and their HSC regulatory function is modified by sympathectomy or by treatment with G-CSF (which downregulates HSC ability to express CXCL12, SCF, angiopoietin, IL7, and vascular cell adhesion molecule 1 (VCAM1)) (Wang & Wagers, 2011). Nestin⁺ cells exhibited multilineage differentiation into various mesenchymal cell lineages including osteoblasts (Nagasawa *et al.*, 2011).

Nestin⁺ cells express high levels of genes involved in the regulation of HSCs: Cxcl12, c-kit ligand, angiopoietin-1, interleukin-7, vascular cell adhesion molecule-1 and osteopontin. Recently, it was demonstrated that bone marrow CD169⁺ macrophages are able to maintain the HSCs through CXCL12 levels and through nestin 265⁺ niche cells, which emphasizes the dense crosstalk among various niches (Nakamura-Ishizu & Suda, 2012).

4. The relationship between the endosteal and vascular niches

It is well known that HSC circulation involves HSCs leaving the bone marrow, entering in the vascular system (mobilization), and returning to the bone marrow (homing). However, the underlying physiological function of these events is not well understood (Yin & Li, 2006).

The endosteal niche, localized at the inner surface of the bone cavity and with abundant osteoblasts, might serve as a reservoir for long-term HSC storage in a quiescent state, whereas the vascular niche, which consists of sinusoidal endothelial cell lining blood vessel, provides an environment for short-term HSC proliferation and differentiation. Both niches act together to maintain hematopoietic homeostasis or to restore it after damage (Guerrouahen *et al.*, 2011).

Based on *in vivo* immunofluorescence with signaling lymphocytic activation molecule (SLAM), a family of cell surface receptors, Kiel & Morrison (2006) identified the vascular niche of HSCs in several tissues, also known as the sinusoidal endothelial niche. Though the two kinds of HSCs niches were anatomically and functionally defined, accumulated data suggests that endosteal and vascular niches overlap in both location and function (Figure 1). Three dimension imaging determined that there are abundant vascular structures on the surfaces of trabecular bones, and that those vessels and endosteal surfaces are intimately coupled with each other within a trabecular region (Wang & Wargers, 2011).

The major difference between both microenvironments is the oxygen level. Higher in the vascular niche than in the endosteal niche under hypoxia, HSCs would move to the vascular niche and resume then the cell cycle in order to restore hematopoiesis. HSCs would then return to the endosteal niche where they would again be maintained in the G0 state (Parmar *et al.*, 2007).

Numerous examples of HSC-endothelial cross-talk exist, although most studies have focused on the function of the endothelial cell in HSC homing. Recent investigations have suggested roles for the vascular CAMs E- and P-selectin and VCAM-1 in HSC homing to bone marrow, as well as for the chemokine SDF-1 (Calmone & Sipkins, 2008).

5. HSCs outside their niches

To turn the situation even more complex, HSCs are not static. Although the vast majority of HSCs in adult humans is located in the bone marrow, HSCs show remarkable mobility. In response to specific signals they can exit and re-enter the endosteal bone-marrow HSC niche, processes known as mobilization and homing, respectively (Wilson *et al.*, 2006).

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 clinical practice to mobilize HSCs is the

granulocyte colony-stimulating factor (G-CSF) or its pegylated form (Peg G-CSF) used in a single administration. 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. 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 (Lymperi *et al.*, 2010).

The release of HSCs not only occurs during mobilization but it is also observed during homeostasis, when a small number of HSCs are constantly released into the circulation. Although their precise physiological role remains unclear, they might provide a rapidly accessible source of HSCs to repopulate areas of injured bone marrow (Wilson *et al.*, 2006).

6. HSC niches and disease

The elucidation of the cellular components and molecular effectors of the HSC niche has raised obvious interest on whether analogous regulatory processes are involved in the biology of bone marrow tumors. Increasing evidences point toward critical roles of nonautonomous, microenvironmental factors in the development, progression, and drug resistance of different malignancies evolving in the bone marrow (Carlesso & Cardoso, 2010). Although most hematopoietic malignancies are likely to arise from mutations that inappropriately activate hematopoietic cell proliferation and survival pathways, recent data demonstrate that hematopoiesis can also be dysregulated by alterations in the niche, with defects in HSCs themselves arising secondarily (Wang *et al.*, 2012). The extent of the reliance of these tumors on the microenvironment appears to be dependent upon the type and stage of malignancy. At one extreme is a neoplastic growth that is dependent on dysregulated cell-cell interactions and signalling pathways within the microenvironment. At the other end of the spectrum there are malignancies that exhibit an absolute dependence on normal microenvironmental cues for disease progression, such as the expression of specific cytokines and growth factors (Guerrouahen *et al.*, 2011).

Several studies have provided insights into the role of altered microenvironment signaling leading to myelofibrosis, myeloma, and myelodysplastic syndromes (Noll *et al.*, 2012). Lataillade *et al.* (2008) suggested that an imbalance between endosteal and vascular niches may be important in idiopathic disorder characterized by bone marrow fibrosis (primary myelofibrosis), leading to the development of clonal stem cell proliferation. The most compelling recent example comes from work in which miRNA processing was disrupted in osteoblast precursors and mice developed myelodysplasia, which in rare cases progressed to myeloid leukaemia by 3 weeks of age; notably, HSCs transplanted from these mice into wild-type recipients did not transfer myelodysplasia, indicating that the HSCs were not intrinsically competent to produce pathologic changes (Hosokawa *et al.*, 2010).

6.1. Leukemic Stem Cells

Leukemic stem cells (LSCs) were first described in 1994. The paradigm of cancer stem cells considers leukemia a hierarchical disease process whose growth is sustained by a rare population of LSCs. LSCs maintain the capacity to self-renewal and give rise to malignant progeny with extensive proliferative potential (Flynn & Kaufman, 2007).

It has been speculated that the transformation involves at least a 2-step process, one mutation blocking differentiation and another event conferring a proliferative advantage to its progeny (figure 2). Other LSCs may result from dedifferentiation of more committed progenitors that reacquire the ability of self-renewal prior to accumulating transforming mutations (Blair *et al.*, 1998).

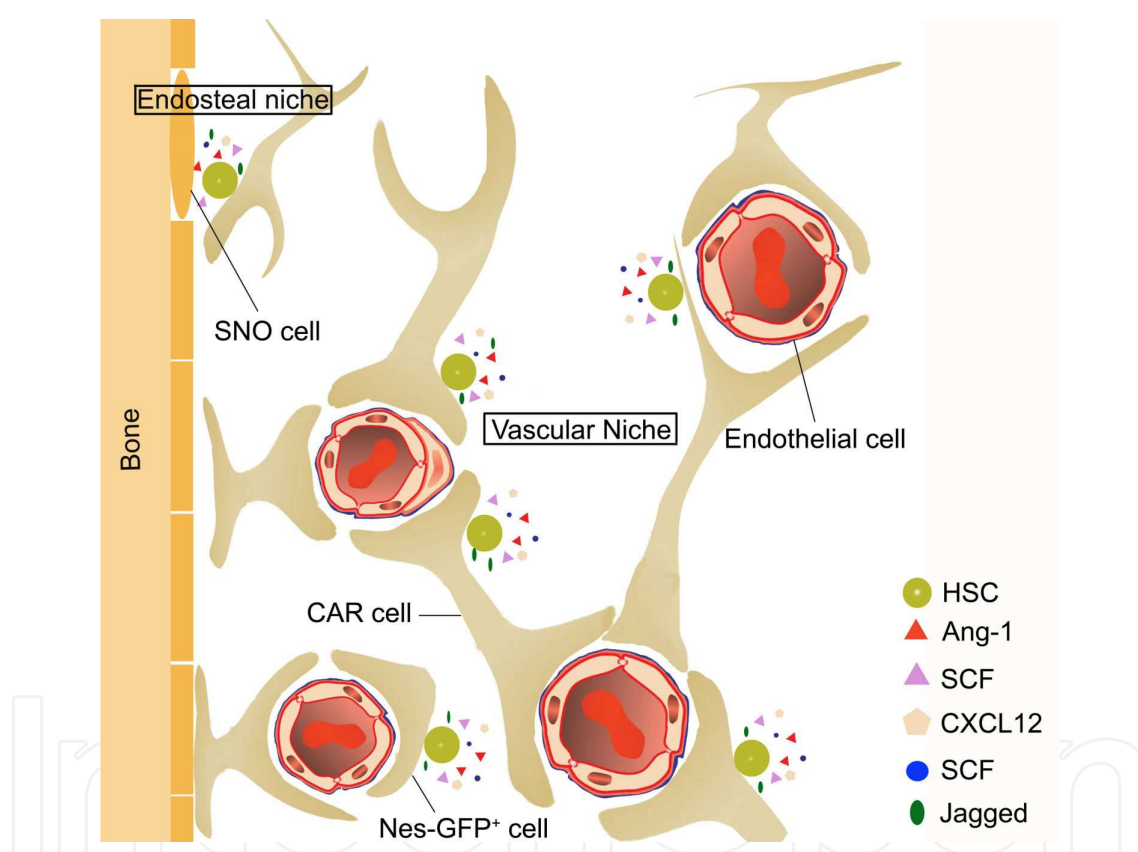


Figure 1. Reticular niches created by mesenchymal progenitors might maintain and regulate HSCs. A model for the localization of HSCs and their association with candidate cell niches in the bone marrow (Modified from Nagasawa *et al.*, 2011).

There is much greater heterogeneity in the phenotype of LSCs than has been previously thought, indicating the inadequacy of the currently used surface antigens or biochemical markers as criteria for LSCs isolation. Evidences from the literature suggest that LSCs are a moving target and its identification depends on many factors including the receptiveness of the murine model used in the experimental design. In addition, it is debatable whether results derived from highly artificial animal models could be extrapolated for the situation in human

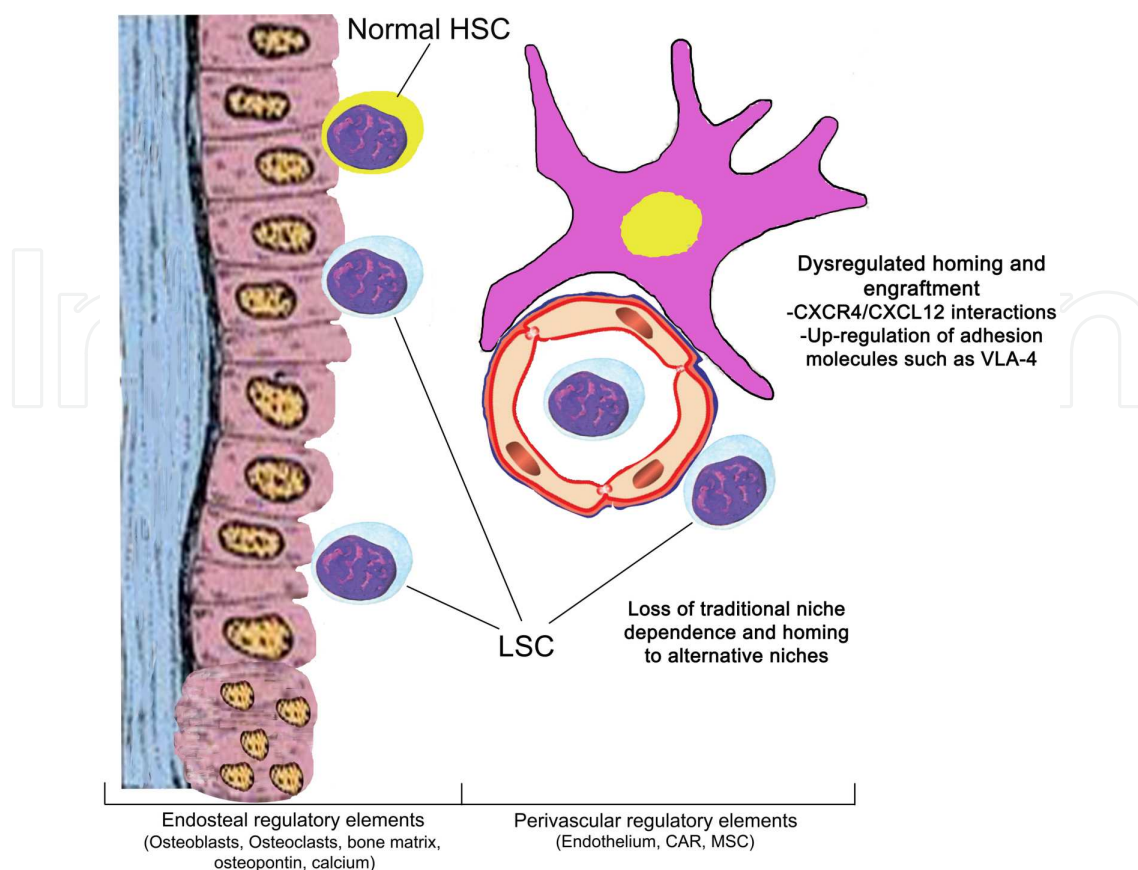


Figure 2. Putative mechanisms for AML stem cell and niche interactions *in vivo*. The niche provides support for self-renewal, quiescence, homing, engraftment, and proliferative potential for HSCs. LSCs may impair the function of the normal HSC niche by direct invasion or secretion of substances such as stem cell factor. LSCs can infiltrate these niches leading to enhanced self-renewal and proliferation, enforced quiescence, and resistance to chemotherapeutic agents. (Modified from Lane *et al.*, 2009).

(Lutz *et al.*, 2012). So far there are only few data analyzing the diversity of LSC in individual patients with acute myeloid leukemia (AML). It has been shown that CD34⁺CD38⁻ subpopulations are heterogeneous in the distribution of mutations compared to the whole blast population at diagnosis. The situation might be similar to the genetic heterogeneity detected in childhood acute lymphoblastic leukemia (Anderson *et al.*, 2011).

In BCR-ABL-associated leukemias, the transformation occurs at the stem cell and progenitor cell level depending on the phenotype and fusion transcript isoform (Castor *et al.*, 2005). It is a population of highly quiescent HSCs expressing BCR-ABL1 that can be isolated from untreated chronic myeloid leukemia (CML) patients and from imatinib-treated CML patients. These quiescent, non-proliferating CD34⁺ CML cells have been shown to be resistant to a range of pro-apoptotic stimuli including chemotherapy and tyrosine kinase inhibition with imatinib. The quiescent BCR-ABL1-expressing HSCs can be regarded as LSCs. By way of comparison, proliferating CD34⁺ progenitors in CML are sensitive to imatinib-induced apoptosis that is significantly mediated by the pro-apoptotic BCL-2 family proteins Bim and Bad (Kuroda *et al.*, 2006; Ng, 2012).

In analogy to normal HSC, LSC also need the marrow niche for their malignant self-renewal and dormant state. Perturbing the binding of LSC to the marrow niche through disruption of the adhesive forces might therefore “mobilize” LSC from their protective environment. Molecules such as CD44, CXCR4, N-cadherin, among others, appear to play significant regulatory roles for HSC and LSC trafficking, signaling and homing to their marrow niche (Sugiyama *et al.*, 2006; Spoo *et al.*, 2007; Teicher & Fricker, 2010; Lutz *et al.*, 2012). LSC may also hijack these pathways in a number of ways, for example, up-regulation of the $\alpha 4\beta 1$ integrin, VLA-4, which mediates adhesion to fibronectin and VCAM-1. Patients with undetectable VLA-4 levels on leukemic blasts had an excellent response to chemotherapy, perhaps indicating that this pathway may mediate a stromal influence on sensitivity to chemotherapy (Matsunaga *et al.*, 2003). These data suggest that interactions between VLA-4 on leukemic cells and fibronectin expressed on BM stromal cells may modulate chemotherapy sensitivity (Doan & Chute, 2012). Another example is the CD44, the receptor for hyaluronic acid, which is also important for hematopoietic stem and progenitor cell homing to the vascular niche. In both, a mouse model of chronic myelogenous leukemia and a xenograft model of human AML, treatment with an anti-CD44 antibody resulted in LSC mobilization from the niche, LSC differentiation and LSC eradication (Krause *et al.*, 2006).

6.2. Multiple myeloma

A number of pathways and cell types have been shown to affect the behaviour of both HSCs in normal hematopoiesis and the malignant myeloma plasma cells. It is through these regulated interactions with cell populations and signalling pathways within the bone marrow microenvironment that myeloma cells are believed to ‘hijack’ the normal hematopoietic niche to aid the extensive growth and proliferation of tumour cells (Noll *et al.*, 2012). Multiple myeloma (MM) is characterized by the proliferation of a malignant plasma cell clone, initially located in the bone marrow microenvironment. This illness is unique among hematological malignancies in its capacity to cause great bone destruction, leading to pathologic bone fractures and intractable bone pain. This result is the consequence of an imbalance between osteoblastic and osteoclastic activity induced by MM cells (Corre *et al.*, 2007).

Normal plasma cells are dependent on specific signals from bone marrow stem cells to regulate their differentiation, growth and localization. These same signals are required for myeloma cell growth and survival, supporting the notion that the bone marrow provides a permissive environment for disease development (Degraffi *et al.*, 1993). It is evident that the presence of myeloma cells in the bone marrow modulates the expression of cytokines from stromal cells, which enhances their ability to modify the microenvironment to support malignant growth (Noll *et al.*, 2012).

7. Conclusion

During the past few years, the theoretical concept of a specific stem cell microenvironment that was proposed in the 1960s and 1970s, has finally received greater attention. As mentioned,

pinpointing the exact location of the hematopoietic stem cell *in vivo* within the bone marrow is difficult, despite advancements in immunohistochemistry, genetic marking of cells, and *in vivo* imaging. Early studies showed that hematopoietic progenitor and stem cells were highly present near the endosteal bone surface, whereas more mature cells were selectively localized centrally within the bone marrow cavity.

The development of hematologic malignancies may be a multi-step process involving mutations both in the hematopoietic cells and/or in cells present in the supportive microenvironment. Targeting the niche-HSCs, niche-leukemic cells, or niche itself in hematopoietic malignancies is an attractive potential addition to the therapeutic possibilities. The challenge of stem cell biology is to translate the expansion of biological insights into clinically meaningful improvements for patients with hematological malignancies and related disorders.

Author details

Sergio P. Bydlowski, Debora Levy, Jorge M.L. Ruiz and Juliana Pereira

Laboratory of Genetics and Molecular Hematology, Department of Medicine, University of São Paulo School of Medicine, São Paulo/SP,, Brazil

References

- [1] Anderson, K, Lutz, C, Van Delft, F. W, Bateman, C. M, Guo, Y, Colman, S. M, Kemp-ski, H, Moorman, A. V, Titley, I, Swansbury, J, Kearney, L, Enver, T, & Greaves, M. Genetic variegation of clonal architecture and propagating cells in leukaemia. *Nature*. (2011). , 469, 356-361.
- [2] Audet, J, Miller, C. L, Eaves, C. J, & Piret, J. M. Common and distinct features of cytokine effects on hematopoietic stem and progenitor cells revealed by dose-response surface analysis. *Biotechnol Bioeng*. (2002). , 80, 393-404.
- [3] Avecilla, S. T, Hattori, K, Heissig, B, Tejada, R, Liao, F, Shido, K, Jin, D. K, Dias, S, Zhang, F, Hartman, T. E, Hackett, N. R, Crystal, R. G, Witte, L, Hicklin, D. J, Bohlen, P, Eaton, D, Lyden, D, De Sauvage, F, & Rafii, S. Chemokine-mediated interaction of hematopoietic progenitors with the bone marrow vascular niche is required for thrombopoiesis. *Nat Med*. (2004). , 10, 64-71.
- [4] Blair, A, Hogge, D. E, & Sutherland, H. J. Most acute myeloid leukemia progenitor cells with long-term proliferative ability *in vitro* and *in vivo* have the phenotype CD34/CD71-/HLA-DR-. *Blood*. (1998). , 92, 4325-4335.
- [5] Butler, J. M, Nolan, D. J, Vertes, E. L, Varnum-finney, B, Kobayashi, H, Hooper, A. T, Seandel, M, Shido, K, White, I. A, Kobayashi, M, Witte, L, May, C, Shawber, C, Ki-

- mura, Y, Kitajewski, J, Rosenwaks, Z, Bernstein, I. D, & Rafii, S. Endothelial cells are essential for the self-renewal and repopulation of Notch-dependent hematopoietic stem cells. *Cell Stem Cell*. (2011). , 6, 251-264.
- [6] Can, A. Haematopoietic stem cells niches: interrelations between structure and function. *Transfus Apher Sci*. (2008). , 38, 261-268.
- [7] Carlesso, N, & Cardoso, A. A. Stem cell regulatory niches and their role in normal and malignant hematopoiesis. *Curr Opin Hematol*. (2010). , 17, 281-286.
- [8] Castor, A, Nilsson, L, Astrand-grundström, I, Buitenhuis, M, Ramirez, C, Anderson, K, Strömbeck, B, Garwicz, S, Békássy, A. N, Schmiegelow, K, Lausen, B, Hokland, P, Lehmann, S, Juliusson, G, Johansson, B, & Jacobsen, S. E. Distinct patterns of hematopoietic stem cell involvement in acute lymphoblastic leukemia. *Nat Med*. (2005). , 11, 630-637.
- [9] Chotinantakul, K, & Leraanansaksiri, W. Hematopoietic stem cell development, niches, and signaling pathways. *Bone Marrow Res*. (2012).
- [10] Corre, J, Mahtouk, K, Attal, M, Gadelorge, M, Huynh, A, Fleury-cappellesso, S, Danho, C, Laharrague, P, Klein, B, Rème, T, & Bourin, P. Bone marrow mesenchymal stem cells are abnormal in multiple myeloma. *Leukemia*. (2007). , 21, 1079-1088.
- [11] Coskun, S, & Hirschi, K. K. Establishment and regulation of the HSC niche: Roles of osteoblastic and vascular compartments. *Birth Defects Res C Embryo Today*. (2010). , 90, 229-242.
- [12] Degrassi, A, Hilbert, D. M, Rudikoff, S, Anderson, A. O, Potter, M, & Coon, H. G. In vitro culture of primary plasmacytomas requires stromal cell feeder layers. *Proc Natl Acad Sci USA*. (1993). , 90, 2060-2064.
- [13] Doan, P. L, & Chute, J. P. The vascular niche: home for normal and malignant hematopoietic stem cells. *Leukemia*. (2012). , 26, 54-62.
- [14] Flynn, C. M, & Kaufman, D. S. Donor cell leukemia: insight into cancer stem cells and the stem cell niche. *Blood*. (2007). , 109, 2688-2692.
- [15] Frisch, B. J, Porter, R. L, & Calvi, L. M. Hematopoietic niche and bone meet. *Curr Opin Support Palliat Care*. (2008). , 2, 211-217.
- [16] Guerrouahen, B. S, Al-hijji, I, & Tabrizi, A. R. Osteoblastic and vascular endothelial niches, their control on normal hematopoietic stem cells, and their consequences on the development of leukemia. *Stem Cells Int*. (2011).
- [17] Hosokawa, K, Arai, F, Yoshihara, H, Iwasaki, H, Hembree, M, Yin, T, Nakamura, Y, Gomei, Y, Takubo, K, Shiama, H, Matsuoka, S, Li, L, & Suda, T. Cadherin-based adhesion is a potential target for niche manipulation to protect hematopoietic stem cells in adult bone marrow. *Cell Stem Cell*. (2010). , 6, 194-198.

- [18] Kiel, M. J, & Morrison, S. J. Maintaining hematopoietic stem cells in the vascular niche. *Immunity*. (2006). , 25, 862-864.
- [19] Kollet, O, Dar, A, Shivtiel, S, Kalinkovich, A, Lapid, K, Sztainberg, Y, Tesio, M, Samstein, R. M, Goichberg, P, Spiegel, A, Elson, A, & Lapidot, T. Osteoclasts degrade endosteal components and promote mobilization of hematopoietic progenitor cells. *Nat. Med.* (2006). , 12, 657-664.
- [20] Krause, D. S, Lazarides, K, Von Andrian, U. H, & Van Etten, R. A. Requirement for CD44 in homing and engraftment of BCR-ABL-expressing leukemic stem cells. *Nat Med.* (2006). , 12, 1175-1180.
- [21] Kuroda, J, Puthalakath, H, Cragg, M. S, et al. Bim and Bad mediate imatinib-induced killing of Bcr/Abl+ leukemic cells, and resistance due to their loss is overcome by a BH3 mimetic. *Proc Natl Acad Sci USA* (2006). , 103, 14907-14912.
- [22] Lane, S. W, Scadden, D. T, & Gilliland, D. G. The leukemic stem cell niche: current concepts and therapeutic opportunities. *Blood*. (2009). , 114, 1150-1157.
- [23] Lataillade, J. J, Pierre-louis, O, Hasselbalch, H. C, Uzan, G, Jasmin, C, & Martyré, M. C. Le Bousse-Kerdilès MC; French INSERM and the European EUMNET Networks on Myelofibrosis. Does primary myelofibrosis involve a defective stem cell niche? From concept to evidence. *Blood*. (2008). , 112, 3026-3035.
- [24] Lilly, A. J, Johnson, W. E, & Bunce, C. M. The haematopoietic stem cell niche: new insights into the mechanisms regulating haematopoietic stem cell behaviour. *Stem Cells Int.* (2011).
- [25] Lutz, C, Hoang, V. T, Buss, E, & Ho, A. D. Identifying leukemia stem cells- Is it feasible and does it matter? *Cancer Lett.* (2012). Epub ahead of print].
- [26] Lymperi, S, Ferraro, F, & Scadden, D. T. The HSC niche concept has turned 31. Has our knowledge matured? *Ann N Y Acad Sci.* (2010). , 1192, 12-18.
- [27] Matsunaga, T, Takemoto, N, Sato, T, Takimoto, R, Tanaka, I, Fujimi, A, Akiyama, T, Kuroda, H, Kawano, Y, Kobune, M, Kato, J, Hirayama, Y, Sakamaki, S, Kohda, K, Miyake, K, & Niitsu, Y. Interaction between leukemic-cell VLA-4 and stromal fibronectin is a decisive factor for minimal residual disease of acute myelogenous leukemia. *Nat Med.* (2003). , 9, 1158-1165.
- [28] Nagasawa, T, Omatsu, Y, & Sugiyama, T. Control of hematopoietic stem cells by the bone marrow stromal niche: the role of reticular cells. *Trends Immunol.* (2011). , 32, 315-320.
- [29] Nakamura-ishizu, A, & Suda, T. Hematopoietic stem cell niche: An interplay among a repertoire of multiple functional niches. *Biochim Biophys Acta.* (2012). Epub ahead of print].

- [30] Noll, J. E, Williams, S. A, Purton, L. E, & Zannettino, A. C. Tug of war in the haematopoietic stem cell niche: do myeloma plasma cells compete for the HSC niche? *Blood Cancer J.* (2012). e91.
- [31] Oh, I. H, & Kwon, K. R. Concise review: multiple niches for hematopoietic stem cell regulations. *Stem Cells.* (2010). , 28, 1243-1249.
- [32] Parmar, K, Mauch, P, Vergilio, J. A, Sackstein, R, & Down, J. D. Distribution of hematopoietic stem cells in the bone marrow according to regional hypoxia. *Proc Natl Acad Sci USA.* (2007). , 104, 5431-5436.
- [33] Ratajczak, M. Z, Zuba-surma, E, Kucia, M, Reza, R, Wojakowski, W, & Ratajczak, J. The pleiotropic effects of the SDF-1-CXCR4 axis in organogenesis, regeneration and tumorigenesis. *Leukemia.* (2006). , 20, 1915-1924.
- [34] Renström, J, Kröger, M, Peschel, C, & Oostendorp, R. A. How the niche regulates hematopoietic stem cells. *Chem Biol Interact.* (2010). , 184, 7-15.
- [35] Schofield, R. The relationship between the spleen colony-forming cell and the haematopoietic stem cell. *Blood Cells.* (1978). , 4, 7-25.
- [36] Shen, Y, & Nilsson, S. K. Bone, microenvironment and hematopoiesis. *Curr Opin Hematol.* (2012). , 19, 250-255.
- [37] Spoo, A. C, Lübbert, M, Wierda, W. G, & Burger, J. A. CXCR4 is a prognostic marker in acute myelogenous leukemia. *Blood.* (2007). , 109, 786-791.
- [38] Sugiyama, T, Kohara, H, Noda, M, & Nagasawa, T. Maintenance of the hematopoietic stem cell pool by CXCL12-CXCR4 chemokine signaling in bone marrow stromal cell niches. *Immunity.* (2006). , 25, 977-988.
- [39] Sugiyama, T, & Nagasawa, T. Bone marrow niches for hematopoietic stem cells and immune cells. *Inflamm Allergy Drug Targets.* (2012). , 11, 201-206.
- [40] Teicher, B. A, & Fricker, S. P. CXCL12 (SDF-1)/CXCR4 pathway in cancer. *Clin Cancer Res.* (2010). , 16, 2927-2931.
- [41] ter Huurne M, Figdor CG, Torensma R. Hematopoietic stem cells are coordinated by the molecular cues of the endosteal niche. *Stem Cells Dev.* (2010). , 19, 1131-1141.
- [42] Wang, H, Zhang, P, Liu, L, & Zou, L. Hierarchical organization and regulation of the hematopoietic stem cell osteoblastic niche. *Crit Rev Oncol Hematol.* (2012). Epub ahead of print]
- [43] Wang, L. D, & Wagers, A. J. Dynamic niches in the origination and differentiation of haematopoietic stem cells. *Nat Rev Mol Cell Biol.* (2011). , 12, 643-655.
- [44] Wilson, A, & Trumpp, A. Bone-marrow haematopoietic-stem-cell niches. *Nat Rev Immunol.* (2006). , 6, 93-106.
- [45] Yin, T, & Li, L. The stem cell niches in bone. *J Clin Invest.* (2006). , 116, 1195-1201.

