Niche heterogeneity in the bone marrow

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Abstract

In adult mammals, hematopoietic stem cells (HSCs) are defined by their abilities to self-renew and to differentiate to form all blood cell lineages. These rare multipotent cells occupy specific locations in the bone marrow microenvironment. The specific microenvironment regulating HSCs, commonly referred to as the niche, comprises multiple cell types whose exact contributions are under active investigation. Understanding cellular cross talk involving HSCs in the bone marrow microenvironment is of fundamental importance for harnessing therapies against benign and malignant blood diseases. In this review, we summarize and evaluate recent advances in our understanding of niche heterogeneity and its influence on HSC function.

Keywords

Introduction

Hematopoietic stem cells (HSCs) represent a rare subpopulation of hematopoietic cells, mostly residing in the bone marrow (BM),[1,2] that reign at the top of the hematopoietic hierarchy. These cells are endowed with regulated quiescence[3,4] and a capacity for long-lived self-renewal that preserves the multipotency of mother cells and sustains the generation of all blood cell types throughout life.[5–10] Their capacity to rebuild the entire adult hematopoietic system makes HSCs invaluable for the treatment of multiple hematopoietic disorders. For several decades, the therapeutic potential of HSCs has been applied to regenerate the hematopoietic system via BM transplantation procedures.[11] Understanding the signaling mechanisms that determine HSC fate will be crucial for the success of clinical applications. Recent investigations using genetically modified mouse models suggest that decisions of HSC self-renewal and multilineage differentiation are dependent on the interaction with the surrounding microenvironment, also termed *niche.*[12–14] Thus, proquiescence, prodifferentiation or pro-self-renewal microenvironments define HSC fate.[15,16] Experimental evidence has shown that deregulation of those microenvironmental regulatory mechanisms plays a key pathogenic role in a variety of hematopoietic diseases.[5]

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In recent years, several cell types have been identified as potential niche-supporting cells for HSCs, regulating HSC activity by supplying various cytokines and retention factors. Here, we present an overview of the current knowledge on the variety of BM cell types and their effects on HSCs.

Heterogeneity of HSCs and niches

HSCs represent a functionally heterogeneous cell population in their degree of self-renewal,[17,18] life span,[19–21] and differentiation capabilities.[22] Self-renewal heterogeneity is manifested by distinct capacities of long-term (LT-HSC), intermediate-term (IT-HSC), and short-term repopulating HSCs (ST-HSC),[23] which have been distinguished by differential abilities to engraft *in vivo* into irradiated hosts and to maintain multilineage hematopoiesis for extended time periods and/or by serial transplantation.[24] A separate challenge for isolating HSC subpopulations is that they may represent a continuum of states of the same cell, which may be challenging to isolate, although a few markers have been shown to define distinct properties, such as CD150 for LT-HSCs,[25,26] integrin α2 (CD49b) for IT-HSCs,[27] or platelet integrin CD41 (also known as Itga2b) for myeloid-biased adult HSCs.[28]

Single purified HSCs exhibit large fluctuations in their contributions to myeloid and lymphoid lineages.[19] Subsequent studies demonstrated distinct biases of HSCs, with consistent preponderance to generate lymphoid or myeloid cells.[29–31] Interestingly, on the basis of Hoechst dye–efflux capability, myeloid- and lymphoid-biased HSC subsets differ in their responsiveness to TGF-ß1. This cytokine induces proliferation of myeloid-biased HSCs while inhibiting proliferation of lymphoid-biased HSCs.[32] More recently, a platelet-biased HSC subset was identified through the use of a von Willebrand factor (vWF)–EGFP mouse system.[33] High expression of vWF, a blood glycoprotein mediating platelet aggregation, was reported in HSC-enriched BM cells.[26] Transplantation of vWF–EGFP+ and vWF–EGFP− cells from the CD150+CD48−CD34− KSL fraction of adult BM achieved long-term hematopoietic reconstitution in recipient mice. This study also suggested that vWF+ HSCs are primed toward the megakaryocytic lineage.[33]

Very little is known about the extrinsic regulation of HSC subpopulations. For instance, it is unclear whether the niches for lymphoid-, myeloid-, or megakaryocyte-biased HSCs differ. The functional heterogeneity of HSCs points to the potential for matching heterogeneity in the microenvironmental influences that support the function and behavior of these HSC subsets. The reader is referred to excellent reviews that discuss these HSC subsets in detail.[34–36] The remainder of the review will focus on niche heterogeneity.

The anatomy of the BM may shed light on the specific microenvironments where HSCs may reside and are regulated. BM is found within the central cavities of long and axial bones. The trabecular regions of the metaphysis have been shown to be the preferred site of HSC homing compared to the epiphysis or diaphysis.[37] The inner surface of the bone cavities is covered by an endosteal lining consisting of osteoblasts, osteoclasts, and a single layer of flat bone-lining cells supported by a thin layer of reticular connective tissue. The endosteal region may present a greater concentration of free calcium ions from continuous bone remodeling.[38,39] Several studies have noted that HSCs tend to localize peripherally near the

bone surface rather than in the central medullary regions.[38,40,41] Moreover, it has been suggested that HSCs at the endosteal location have greater self-renewal capacity than those in the central marrow cavity,[42] suggesting the presence of a distinct microenvironment in this region. However, other recent analyses have suggested that HSCs may be randomly distributed in the BM.[43] Interestingly, aged HSCs localize to sites further away from the endosteum compared with young HSCs,[44] suggesting that HSC location is affected by aging.

The BM is served by numerous blood vessels of various sizes entering it through the cortical bone via nutrient canals.[45] Lymphatic drainage is absent in the BM.[46] The blood supplies of the bone and BM are interconnected through an endosteal network of vessels. Arteries give rise to a multitude of small, thin-walled arterioles that extend outwardly toward the cortical bone and sinusoids that pervade the central and endosteal marrow. Arterioles are small resistance vessels that, unlike other vessels in the BM, are wrapped circumferentially by one or more layers of smooth muscle cells.[47,48] They are preferentially located close to the endosteal region of the BM.[41] Nerve bundles follow the arterioles, with branches serving smooth muscle cells or terminating in the hematopoietic tissue among hematopoietic cells.[49] The sinusoids form a permeable barrier for the passage of mature blood cells into the circulation. In contrast to arterioles, sinusoids are evenly distributed through the whole BM cavity and are not innervated. Both BM arteriolar and sinusoidal endothelial cells are surrounded by perivascular cells.[50]

Besides blood vessels and nerves, the BM tissue consists of a variety of cellular subtypes among hematopoietic and non-hematopoietic cells. Hematopoietic cells are most likely not randomly arranged but demonstrate a specific organization within the tissue.[51] For instance, erythropoiesis takes place in distinct anatomical units (erythroblastic islands),[52–54] and a subset of HSCs is located near megakaryocytes.[55,56]

A niche supporting HSCs identified in close proximity to blood vessels in the adult BM has been called the perivascular niche.[25,41] The perivascular niche itself is heterogeneous and contains distinct cell types. A recent study showed that dormant (quiescent) HSCs reside specifically in the proximity of arterioles rather than sinusoids, proposing that there are separate, spatially distinct perivascular niches for quiescent and proliferating HSCs in the BM.[41]

During development, perivascular hematopoietic niches have been also described to be present in other organs, like the placenta[57] and spleen.[25] Additionally, a recent report showed that HSCs expand around fetal liver portal vessels, suggesting that blood vessels provide an adaptive niche, serving hematopoiesis at multiple developmental stages of mammalian life.[58]

Heterogeneity of cells of the niche

Non-hematopoietic types

Osteoblasts—Cells of the osteoblastic lineage have been proposed to function as critical modulators of HSCs in the BM.[59] *In vitro* culture experiments have suggested that

osteoblastic cell lines can expand the number of HSCs two- to fourfold.[60] In addition, when co-transplanted with HSCs, osteoblasts can increase the engraftment rate.[61] Osteoblasts produce a wide array of growth factors and cytokines, important for HSCs maturation.[60,62] Osteopontin, an osteoblast-secreted protein, participates in HSC location and is a negative regulator of their proliferation.[63,64] Furthermore, angiopoietin-1 expressed by osteoblasts has been suggested to regulate HSC numbers through the activation of Tie-2 signaling pathway,[65] while Jagged 1, a Notch receptor ligand, supports an increase in HSC numbers.[66] Mutant mice with conditional deletion of BMP receptor type IA or genetic alteration to produce osteolineage-specific activated PTH led to abnormal bone formation with increased osteoblast numbers that correlated with increased HSC numbers in the BM.[66] Genetic depletion of osteolineage cells by the use of GCV in transgenic mice expressing herpesvirus thymidine kinase gene under the control of a constitutive 2.3-kb fragment of the rat $\alpha(1)$ type I collagen promoter leads to BM hypocellularity and extramedullary hematopoiesis within the spleen and liver.[67] After GCV is withdrawn, osteoblasts reappear in the bone compartment, together with a decrease in extramedullary and a recovery of medullary hematopoiesis.[67]

Since constitutive promoter expression may not be specific to mature osteoblasts but could be expressed up to the MSC stage,[68] specificities with careful lineage tracing to assess transgenic expression and recombination are needed to define osteolineage cells. Indeed, adipo-osteogenic progenitors[69] and Nestin+ cells[70] express the osteogenic proteins Runx2 and Osterix. In keeping with this idea, osteoblastic expansion does not always promote HSC expansion in the BM.[71] Strontium, which inhibits both osteoclast resorbing activity and osteoblast bone-forming activity,[72] did not increase the number or frequency of HSCs when administered in doses higher than normally detected in the body.[71] Osteocytes, derived from osteoblasts that became embedded within the bone matrix, appear to have an inhibitory effect on HSC support.[73] More recent studies have shown that cells of the osteoblastic lineage may support lymphopoiesis. Elimination of osteoblasts in *Col2.3-TK* transgenic mice depleted pre-pro-B and pro-B cells from the BM[74] without affecting the HSCs.[75] Depleting CXCL12 from osteoblasts in *Col2.3-cre* mice leads to loss of lymphoid progenitors in the BM without affecting the number of HSCs.[76] Thus, the exact function of osteoblasts in hematopoiesis remains unclear; most recent studies indicate that they are dispensable for HSC maintenance and more important to lymphoid progenitors.

Endothelial cells—The endothelium forms the inner cellular lining of blood vessels.[77] Because most HSCs were found to be associated with blood vessels, endothelial cells were suggested to play important roles in HSC maintenance in sinusoids.[78] An intact vasculature is necessary for HSC recovery and hematopoietic reconstitution following total body irradiation and BM transplantation.[79–81] Several studies described the expansion of HSCs on an endothelial cell feeder system *in vitro*.[82–86] In addition, BM endothelial cells have been proposed to produce soluble factors that have the ability to promote HSCs self-renewal and regeneration *in vivo*.[80,81,87–90]

HSCs are found in close contact with endothelial cells at all developmental stages. Endothelial cells harvested from embryonic tissues have been shown to support the expansion of adult HSC cells *in vitro*.[91,92] On the contrary, endothelial cells isolated from

adult non-hematopoietic organs do not display an HSC-supportive activity *in vitro*.[93] These observations indicate tissue-specific functional characteristics of endothelial cells.

Deletion of glycoprotein 130 from endothelial and hematopoietic cells with *Tie2-cre* mice resulted in BM dysfunction and severe anemia by adulthood. Hematopoietic defects remained after transplantation of wild-type BM into irradiated glycoprotein 130–deficient mice, while normal hematopoiesis was reconstituted after transplantation of glycoprotein 130–deficient BM into irradiated wild-type mice, indicating that glycoprotein 130 expression on endothelial cells rather than hematopoietic cells influenced hematopoiesis.[94] Deletion of *Scf* in the same *Tie2-cre* mice led to reduced HSC frequencies with diminished repopulation capacities after BM transplantation, suggesting that SCF derived from endothelial cells contributes to HSC maintenance.[95] Additionally, despite the fact that depletion of CXCL12 from endothelial cells using the same mouse model had no effect on the number of HSCs, it resulted in a slight decrease of long-term repopulating activity.[96]

Endothelial cells are heterogeneous in their morphology, gene expression, antigen composition, distribution, and function. Endothelial cell phenotypes vary between different tissues, as well as between different segments of the vasculature within the same tissue.[97,98] It remains unknown, for instance, whether arteriolar and sinusoidal endothelial cells differ. Elucidating their molecular differences in the BM may reveal novel concepts about these cells' role in the HSC niche.[98]

Pericytes—Pericytes have long projections that encircle the blood vessel wall in almost all tissues.[99–106] They are defined by their anatomical locations in combination with several molecular markers, such as platelet-derived growth factor receptor β (PDGFRβ), CD146, neuron-glial 2 (NG2), αSMA, desmin, and Nestin. However, marker expression is highly dependent on the tissue type, and could often be affected by the pathologic state of the organ.[99]

Pericytes have been suggested to influence HSCs in both mice and humans.[70,95,107] Using *Nestin–GFP* transgenic mice, Nestin+ perivascular cells have been defined as central components of the HSC niche, regulating HSCs via the expression of C-X-C motif chemokine 12 (CXCL12) and stem cell factor (SCF)[70, 108]. *In vivo* ablation of those cells in the BM significantly reduces the number of HSCs.[70] Cells located in a pericytic position close to the vasculature enriched in CXCL12 have been described and named CXCL-12 abundant reticular (CAR) cells.[50] The transcription factor forkhead box C1 (FoxC1) in CAR cells has recently been identified as essential for maintenance of HSCs *in vivo*.[109] Selective ablation of CAR cells in the BM leads to reduction of HSCs.[69] Additionally, PDGFRα+Sca-1+ (PαS) cells,[110] located in the arterial perivascular space,[111] and leptin receptor–expressing pericytes have been suggested to regulate HSC maintenance in the BM.[95,96] These cells exhibit common characteristics in that leptin receptor+ stromal cells overlap with CAR cells[76] and represent a large subset (nearly 90%) of Nestin–GFP+ cells in the BM. Nestin–GFP+ cells also overlap with PαS cells, although most PαS cells are associated with the bone itself (most marrow Nestin–GFP+ cells do not express Sca-1).[108]

There are at least two varieties of BM pericytes according to their location in the blood vessels: arteriolar and sinusoidal.[41] Sinusoids are structurally different from arterioles in that they are lined by a single layer of endothelium, while arterioles are thicker-walled blood vessels.[112] Arteriolar and sinusoidal pericytes can be separated in *Nestin–GFP* transgenic mice according to *Nestin-GFP* transgene expression level.[41] Sinusoidal pericytes are more numerous and reticular in shape. They express lower levels of the *Nestin–GFP* transgene, whereas rare arteriolar Nestin–GFP[bright] pericytes exhibit a classic pericyte morphology. Additionally, arteriolar pericytes express the pericytic marker NG2 proteoglycan, but do not express leptin receptor; while sinusoidal pericytes express leptin receptor, but lack NG2 expression.[41] The embryonic origin and the developmental relationships of BM pericyte subpopulations have yet to be elucidated. Interestingly, an evaluation of the cell cycle status demonstrated that arteriolar pericytes are largely quiescent.[41] Tridimensional imaging of the adult mouse BM has revealed that the majority of dormant HSCs are situated close to arterioles; and genetic depletion of arteriolar pericytes resulted in migration of HSCs away from the arterioles, switching them into non-quiescent status.[41] This suggests that arteriolar pericytes promote HSC dormancy, essential for HSC maintenance in the BM.[41] Nevertheless, the molecular mechanisms by which arteriolar pericytes regulate HSC quiescence remain to be clearly defined.

Adipocytes—It has been suggested that BM fat is unlike white and brown fat of other tissues.[113–115] Adipocytes appear dispersed within the BM, instead of being grouped into lobules, and are smaller than visceral and subcutaneous adipocytes.[116,117] Although older studies suggested that adipocytes were passive occupants of the BM,[118] simply filling the spaces after trabecular bone loss, a regulatory role in the BM has emerged with recent studies.[113,118,119] A specific marker for BM adipocytes has not yet been determined, but there are several differentially expressed genes in BM adipocytes compared to subcutaneous and epididymal adipocytes.[120,121] A reduction of adipocyte numbers with increased size has been noted with disease and aging in the BM.[113,119,122–125] This also has been associated with a decrease in cellularity[126] and induction of myeloid-biased differentiation in HSCs.[1] Nevertheless, no direct link between an increase in adipose tissue and HSC myeloid bias during aging has been established.

Similar to adipocytes from other tissues, BM adipocytes are able to secrete cytokines, fatty acids, and hormones, and have a potential to influence the function of other neighboring cells in the BM microenvironment via paracrine mechanisms.[119,124,127–130] The details of those mechanisms are still being unraveled. For instance, *in vitro*, BM adipocytes secrete more leptin than subcutaneous adipocytes.[131] Some investigators have suggested that this is attributable to an important role of leptin in myelopoiesis,[132] where, in the diet-induced obesity mouse model, hematopoiesis is enhanced due the high leptin levels in the BM.[130] However, *in vitro* studies differ on their conclusions about the effect of adipocytes on HSCs. While some studies show that adipocyte negative regulation can balance the positive effects of other cellular components of the BM niche on HSCs,[133] others suggest that adipocytes can support HSC growth and differentiation *in vitro*.[134,135] However, alterations of adipocyte number and volume *in vivo* have been reported to have no effect on HSCs.[134,135]

A great number of studies indicate that adipocytes inhibit HSCs function as well as hematopoietic reconstitution.[136–138] Lipid-filled BM adipocytes have been connected to the repression of growth and differentiation of HSCs[136,139] and considered negative regulators of the hematopoietic niche.[69,140] Hematopoietic recovery is improved following chemotherapy in mice with chemically inhibited adipogenesis.[141] In mouse tail vertebrae, where BM cavities are densely filled with adipocytes, the few HSCs detected are largely quiescent.[136] The adipocyte suppressive function has been attributed to the reduced production of granulocyte colony-stimulating factors (GM-CSF and G-CSF) and to the increased secretion of lipocalin-2 and neuropilin.[136,142,143] Interestingly, at the same time that adipocytes prevent HSC expansion, they seem to positively affect HSCs via secretion of adiponectin and TNFα,[144,145] playing a role in preserving the hematopoietic stem cell pool.[136] Whether the role of BM adipocytes in the HSC niche differs under various physiological conditions, including aging or obesity, remains unclear.

Schwann cells—Schwann cells are the principal glial cells of the peripheral nervous system. In the BM, they are present in their unmyelinated form associated with sympathetic and sensory nerve fibers.[70,146,147] Until recently, unmyelinated Schwann cells received relatively little scientific attention, with only a poor understanding having developed of their function outside the nervous system. Schwann cells maintain the ability to revert to an immature phenotype in response to injury and disease and, by doing so, they can then re-enter the cell cycle, proliferate, and affect the microenvironment in which they are located.[148,149] Schwann cells were shown to produce several cytokines,[150] and to express cytokine receptors as well.[151]

Recent studies have suggested that BM Schwann cells regulate the hibernation and activation of HSCs.[152] In that study, using immunohistochemistry, the expression of active TGFβ was proposed to be restricted to BM Schwann cells.[152] BM denervation reduced the number of cells producing active TGFβ, leading to a loss of HSCs from the BM.[152] However, denervation not only affects Schwann cells; for instance, β-adrenergic signals from the sympathetic nervous system have been shown to regulate enforced[49] and circadian HSC egress.[153] Moreover, in addition to Schwann cells, other cells, including megakaryocytes, produce TGFβ in the BM.[154] TGFβ1 derived from megakaryocytes has been shown to maintain HSC quiescence.[56] Most of BM innervation—and Schwann cell ensheathing of those nerve fibers—runs along arterioles in the BM.[155] As arterioles contain multiple cell types, the identity of the cell promoting HSC quiescence remains unknown. Interestingly, both pericytes and Schwann cells express NG2 proteoglycan and may contribute to the arteriolar HSC niche.[41,156] It will be interesting to ascertain whether BM Schwann cells differ from Schwann cells from other tissues. Successful isolation of BM Schwann cells may enable the discovery of novel niche factors possibly expressed by those cells.

Nerves—Signals from the sympathetic nervous system have been identified as regulatory components of the HSC niche.[13,157,158] Sympathetic nerves produce catecholamines, which are delivered to the BM microenvironment by the blood circulation or by secretion from the nerve endings acting in paracrine signaling.[159] Sympathectomy achieved by treating mice with the neurotoxin 6-hydroxydopamine does not affect HSCs number,[49,153,160,161] but it

impairs mobilization in response to G-CSF.[49] Under steady-state conditions, HSCs egress from the BM to enter the blood circulation predominantly in the morning in rodents (night in humans),[153] and migrate to the tissues during the night in rodents (day in humans).[162–165] Adrenergic signaling reduces CXCL12 expression in the BM.[153,166] Moreover, recent evidence shows that chemotherapy-induced injury of sympathetic nerves in the BM prevents hematopoietic recovery, suggesting that treatment with neuroprotective drugs during chemotherapy would preserve HSC function in the BM niche.[161] Induction of sympathetic neuropathy by malignant cells has recently been demonstrated.[167,168]

HSCs express catecholaminergic receptors, suggesting that they are able to directly respond to signals from the sympathetic nervous system.[169] Treatment of HSCs with dopamine agonists enhances colony formation *in vitro*, albeit only in the presence of G-CSF.[169] Pretreatment of HSCs with dopamine agonists enhances their ability to engraft.[169] Additionally, norepinephrine treatment of HSCs also enhances both colony-formation capabilities *in vitro* and engraftment *in vivo*.[159,169] Additionally, the sympathetic nervous system adjacent to the dorsal aorta plays an important role in HSC specification during development.[170] Overall, these studies suggest a contribution of the sympathetic nervous system in regulating the HSC niche.

Hematopoietic types

Macrophages—Macrophages play diverse roles in the bone and marrow. At the sites of bone remodeling, they are anatomically juxtaposed with endosteal osteoblasts and participate in bone mineralization.[171–173] Radio-resistant macrophages protect the HSC pool from exhaustion by producing prostaglandin E2 after irradiation.[174] BM resident macrophages are defined based on differential expression of several molecular markers, such as Gr-1, F4/80, CD115, and CD169.[175] Their numbers are reduced during G-CSF–induced HSC mobilization, and, following their loss, HSCs egress to the peripheral circulation.[174176]

Macrophages promote HSC retention in the BM by regulating the expression of CXCL12 by Nestin–GFP+ MSCs via a soluble factor secreted by CD169+ macrophages.[54] Recent studies have suggested that this factor was oncostatin M.[177] Thus, macrophages and sympathetic nerves exert the opposite action to the niche, forming a regulatory loop.[54] HSC retention in the BM and the spleen relies at least partially on a ligand for VCAM-1, integrin VLA-4,[178–180] which is expressed by macrophages. A recent study described that macrophages are important players in splenic HSC retention, as depleting macrophages using inducible diphtheria toxin receptor expression at the *CD169* locus mice or silencing VCAM-1 in macrophages caused release of HSCs from the spleen.[181] Additionally, a separate subpopulation of macrophages expressing high levels of α-smooth muscle actin and cyclooxygenase 2 was recently identified. This rare macrophage population synthesizes prostaglandin E2, which increases CXCL12 expression in Nestin-GFP+ MSCs[182] and CXCR4 expression on HSCs,[183] thus improving the survival and maintenance of HSCs in the BM. Moreover, macrophages have been suggested to regulate HSC egress from the BM after phagocytosis of aged neutrophils.[184]

Interestingly, macrophages are also key mediators of the neuroprotective effect of neuropeptide Y, and thus contribute to HSC survival in the BM. Neuropeptide Y regulates

homeostasis in several tissues through Y receptors.[185–187] A recent study shows that neuropeptide Y deficiency impairs HSC survival and BM regeneration. Furthermore, pharmacological elevation of neuropeptide Y prevented the deficits, while neuropeptide Y injection into mice lacking the Y1 receptor specifically in macrophages did not rescue BM dysfunction.[188]

Macrophages are also involved in both steady-state and stress-induced erythropoiesis. *In vivo* macrophage depletion leads to a decreased number of erythroblasts in the BM and induces anemia with characteristics of iron-deficiency anemia, which is not corrected by iron supplementation. Macrophage depletion also delays erythropoietic recovery following acute blood loss, myeloablation, or challenge with hemoglobin-oxidizing phenylhydrazine (PHZ).[53,54] Interestingly, polycythemia vera, which is characterized by elevated erythropoiesis, can be improved via macrophage ablation. Macrophage depletion reduces hematocrit and red blood cell counts in a mouse model of polycythemia vera driven by the JAK2^{V617F} mutation.[54] These studies suggest that macrophages are critical components of erythroid maturation in the steady state, as well as during erythropoietic rescue after stress and disease. It remains unknown how erythroblastic island macrophages differ functionally from other BM resident macrophages. Erythroblastic island macrophages thought to be very large (with diameter exceeding 15 μm) express F4/80 and do not express Mac1;[189] however, a unique molecular marker for erythroblastic island macrophages remains to be discovered. Overall, these findings suggest that macrophages are key components of the BM niche promoting the maintenance and retention of HSCs.

Osteoclasts—Osteoclasts originate from hematopoietic progenitors via mononuclear phagocytes.[190] They are the only cell type capable of bone resorption in the human body, allowing the renewal of the skeleton but also opening space in the BM for hematopoietic cells. Osteoclasts have been suggested to contribute to HSC release via enzyme secretion, enhancing mobilization.[191] On the other hand, it has been hypothesized that osteoclastic bone resorption releases calcium, increasing its concentration at the endosteal region, which attracts and retains HSCs that express calcium-sensing receptors in the BM.[39] Bone resorption also produces active TGFβ, which can act on HSCs.[192] Osteoclast inhibition by bisphosphonates causes a reduction in the number of HSCs and delays hematopoietic recovery.[193] Using a mouse model with loss of osteoclast activity, osteoclasts have been shown to regulate mesenchymal cell differentiation and HSC maintenance.[194]

Megakaryocytes—A subset of HSCs is located in close proximity to megakaryocytes in the BM.[55,195,196] Several mouse models with increased number of megakaryocytes have also demonstrated increased bone mass.[197] Thus, some studies have suggested a complex interaction between megakaryocytes, HSCs, and the osteolineage within the BM. Accordingly, after BM radioablation, host megakaryocytes are recruited to the endosteum, where osteoblasts undergo rapid expansion in response to the secretion of megakaryocyte-derived mesenchymal growth factors, such as platelet-derived growth factor-β (PDGF-β), to promote HSC engraftment and hematopoietic reconstitution after BM transplantation.[198] The migration of megakaryocytes to the endosteum is thought to depend on thrombopoietin

signaling, since the inhibition of c-Mpl reduces megakaryocyte migration after radioablative conditioning.[198]

More recent findings have identified a direct HSC regulation by megakaryocytes in steady-state hematopoiesis.[55,56,195] Ablation of megakaryocytes reduces HSC engraftment and proliferation.[195,198] Thrombopoietin administration to megakaryocyte-depleted mice restores the number of quiescent HSCs,[195] suggesting that thrombopoietin may contribute to regulation of HSCs by megakaryocytes. Megakaryocytes produce high levels of TGFβ, which regulate HSCs.[199] Conditional deletion of *Tgfb1* in megakaryocytes increases HSC activation and proliferation in young mice.[56] In addition, TGFβ injection into megakaryocyte-depleted mice restores HSC quiescence.[56] Under homeostatic conditions, megakaryocytes maintain HSC quiescence through TGFβ signaling; while under stress megakaryocytes promote HSC expansion via FGF-1 production.[56] CXCL4, which is produced by megakaryocytes, negatively regulates HSC proliferation, reduces HSC numbers, and decreases engraftment.[55] An increase in HSC number, proliferation, and repopulating activity was observed in *CXCL4* knockout mice.[55] As megakaryocytes produce multiple cytokines (e.g., thrombopoietin, TGFβ, and CXCL4), it is possible that their effect on HSCs results from the balance of all those and probably more molecules. Interestingly, megakaryocytes physically associate with approximately 20% of HSCs in the BM.[55] It remains to be studied whether the function of those HSCs differs from that of the rest of the HSCs in the BM. Overall, these observations confirm that megakaryocytes serve as HSC-derived niche cells directly regulating HSC function.

Lymphocytes—Lymphocytes, essential for both cell-mediated and antibody-mediated immunity, are widely distributed throughout the BM parenchyma and make up a major fraction of total BM mononuclear cells.[200] Lymphocytes have been suggested to influence hematopoiesis, potentially through direct cellular interactions with the HSCs.[201] Natural killer cells have been suggested to play a negative role in HSC differentiation.[202] Experiments in adult mice harboring a null mutation in the common γ chain indicated that cytokines secreted by activated T cells in the BM modulate normal hematopoiesis.[203] Even though, in the absence of activated BM, CD4+ T cell HSCs can give rise to committed myeloid progenitors, these progenitors exhibit impaired ability to complete their differentiation program and give rise to mature cells.[204] After adoptive transfer of CD4+ T cells, this defective myeloid differentiation is restored in T cell–deficient mice, suggesting that CD4+ T cells are essential to the maintenance of basal hematopoiesis in the BM.[204]

Regulatory T cells make up one third of all CD4+ T cells in the BM.[205,206] Depletion experiments and co-transfer of BM with regulatory T cells indicated that these cells suppress colony formation and myeloid differentiation of HSCs.[207] Moreover, FoxP3+ regulatory T cells colocalize with HSCs in the endosteal surface in the calvarial and trabecular BM, and this colocalization is lost after depletion of regulatory T cells.[208] However, whether this interaction is biologically relevant to the homeostatic HSC maintenance is still unclear. Furthermore, regulatory T cells have been suggested to provide an immune-privileged niche in the BM, protecting HSCs from immune attacks.[208]

Neutrophils—Neutrophils are the most abundant subpopulation of leukocytes, with a BM reserve estimated to be 6×10^{11} in humans and 12×10^7 in mice.[209,210] Neutrophils have short circulating half-life (6–8 h), after which they quickly migrate to tissues where they perform their functions.[209] Serine proteases derived from neutrophils are capable of cleaving several cytokines and receptors essential for HSC retention *in vitro*, including CXCL12,[211] CXCR4,[212] VCAM-1,[213] c-Kit,[214] and SCF,[215] suggesting that activated neutrophils create a proteolytic microenvironment that may contribute to HSC release from the BM. However, it was shown that, in mice lacking these proteases, G-CSF–induced HSC mobilization proceeds normally,[216] suggesting that serine proteases are not essential for BM egress.

G-CSF induces neutrophil expansion in the BM, which may lead to MSC and osteoblast apoptosis and reductions in the expression of factors that are responsible for HSC retention in the BM.[217] However, neutrophil number in the BM does not necessarily correlate with HSC mobilization.[176] Another study showed that depleting circulating neutrophils increased CXCL12-expressing stromal cells number and CXCL12 protein levels, which resulted in enhanced retention of HSCs in the BM.[184] Those effects are lost in mice in which neutrophils do not express CXCR4 and lack tropism to the BM, indicating that these effects may be exerted locally in the BM.[184,218] Ablation of BM macrophages reverses the niche-modulating functions of neutrophils, indicating that the effect of neutrophils on the hematopoietic niche is dependent on macrophages. Together, these data explains how the daily clearance of aged neutrophils in the BM generates signals that affect HSCs in the BM niches.[184]

Conclusions and perspectives

The studies discussed in this review illustrate the contributions of multiple cell populations within the BM microenvironment to the complex regulation of HSC function. The use of sophisticated genetic tools has demonstrated that changes to the niche composition can have profound effects on HSC behavior. Recombination-based technology provides powerful means to interrogate the cellular and molecular components of niches. However, it is completely dependent on the promoter specificity and activity driving Cre, which must be characterized extensively before reaching conclusions about cell specificity or origins. Future clarification of the interactions between HSCs and their microenvironments during embryonic development may lead to improved methods to exploit the clinical potential of HSCs. Procedures to induce HSC self-renewal will benefit from this knowledge. Our increased understanding of healthy HSC niches should foster studies on the altered HSC niches in BM disorders. Targeting the niche itself is an attractive potential possibility for the treatment of hematologic disorders. The balance of extrinsic influences from the supportive niche may also vary under different physiological conditions. Newborn, adult, and aged HSCs have different physiological demands. The exploration of how the BM microenvironment ages will reveal essential information for the treatment of age-related BM illnesses. Likewise, understanding how the niche controls HSC function during stress situations, such as infections, radiotherapy, and chemotherapy, is needed. Recent studies suggest that BM endothelial cells play crucial roles in HSC recovery following radiation injury.[89,219] A big challenge for the future will be to translate animal research into humans.

Improving the availability of human tissue samples will be essential to reach this goal. Enormous advancement has been accomplished in our understanding of the importance and the complexity of the BM microenvironment to HSC function and to the health of the organism as a whole. The best is yet to come.

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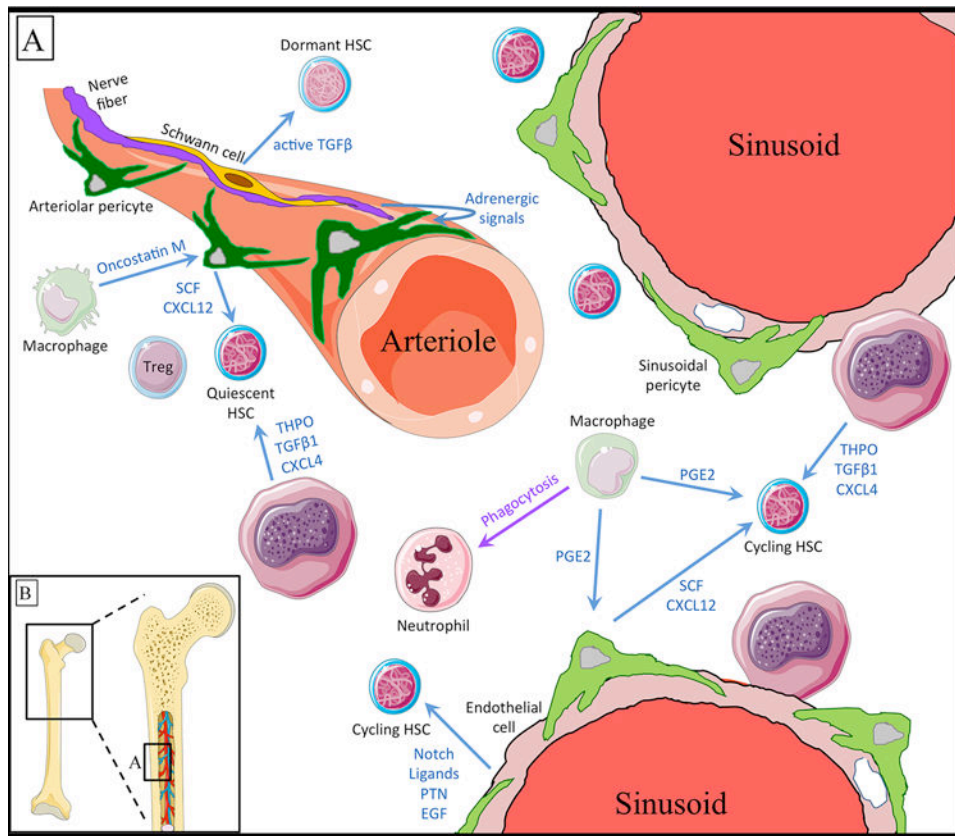
Figure 1.
Diagram illustrating the quiescent arteriolar and the active sinusoidal HSC niches during
BM homeostasis. The BM microenvironment hosts various hematopoietic and non-
hematopoietic cell types, including macrophages, megakaryocytes, lymphocytes,
neutrophils, pericytes, and endothelial and Schwann cells. These cells contribute to the BM
microenvironment and regulate HSCs directly by secretion of cytokines such as CXCL12
and SCF and/or indirectly through signaling via other cells, for example, by prostaglandin
E2, which increases the expression of CXCL12 in perivascular cells. Deeply quiescent
(dormant) HSCs are found around arterioles, while activated HSCs, which are significantly
more abundant than dormant HSCs, are located near sinusoids. TGFβ, transforming growth
factor β; THPO, thrombopoietin; PTN, pleiotrophin; PGE2, prostaglandin E2; EGF,
epidermal growth factor; T_{reg}, CD4+CD25+FOXP3+ regulatory T cell.