A review of bone marrow niche cellular spectrum

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To perform a narrative review on the role of bone marrow (BM) niche in normal hematopoiesis.
MEDLINE databases and Ovid database were searched. The search was performed on 10 October 2018 and included articles published from 2015 to 2018 in English language.
The initial search presented 45 articles, which were included in the study.
Hematopoietic stem cells which produce a variety of hematopoietic lineage cells throughout the life are located in a specialized microenvironment called the 'niche' in the BM where they are governed. Several types of cells in the BM have been suggested to contribute to hematopoietic stem cell niche activity.

Keywords:
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Introduction

For many years, the bone marrow (BM) niche was considered to be little more than an inert scaffold, providing structure for the much more interesting hematopoietic stem and progenitor cell activity contained within. In the past decade, however, the BM microenvironment has been recognized to be a vibrant living tissue that, in addition to important homeostatic roles in hematopoiesis, can aid neoplastic disease processes [1].

The niche hypothesis was proposed by Ray Schofield in 1978. By noticing that CFU-S 'stem cells' have less robust reconstitution capacity in irradiated mice compared with cells from BM, he hypothesized the existence of a BM niche that preserves stem cells [2].

An intricate and dynamic relationship between hematopoietic stem cell (HSC) 'seeds' and the niche 'soil' helps to determine whether the product of hematopoiesis will be a healthy, useful mature blood cells or instead an overgrowth of developmentally stunted, immature, dysfunctional dysplastic blasts – akin to hematological 'weeds' [3].

The interest in the study of the HSCs niche is accurate characterization of the cell populations and factors produced by them, responsible for HSCs maintenance *in vivo* [4].

The stem cell niche spectrum

The anatomy of the BM may unravel the specific niches where HSCs live and are regulated [5].

Osteoblasts

Cells of the osteoblastic lineage have been proposed to function as significant modulators of HSCs in the BM. *In vitro* culture experiments have suggested that osteoblastic cell lines can expand the number of HSCs two fold to four fold [6]. Additionally, when cotransplanted with HSCs, osteoblasts can increase the engraftment rate. Osteoblasts secrete a wide group of growth factors and cytokines, important for HSC maturation. Osteopontin, an osteoblast-secreted protein, contributes to HSC location and is a negative regulator of their proliferation [7].

Furthermore, angiopoietin-1 expressed by osteoblasts has been proposed to regulate HSC numbers through the activation of the Tie-2 signaling pathway, whereas Jagged 1, a Notch receptor ligand, supports an increase in HSC numbers [8].

Osteocytes, derived from osteoblasts that become embedded within the bone matrix, appear to have an inhibitory effect on HSC support [9].

It had been shown that cells of the osteoblastic lineage may support lymphopoiesis. Thus, the precise function of osteoblasts in hematopoiesis remains indistinct; subsequent studies indicate that they are dispensable for HSC maintenance and more important to lymphoid progenitors.

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Endothelial cells

Vascular endothelial cells isolated from BM are known to promote the proliferation and differentiation of human CD34+ progenitor cells *in vitro* [10].

Blocking angiogenic activity of endothelial cells by neutralizing vascular endothelial-cadherin and vascular endothelial growth factor receptor-2 impaired supportive function of endothelial cells to long-term HSCs [11].

Despite the relatively small amount of niche factor expression, conditional deletion of niche factors, CXL12 or SCF, from endothelial cells led to the decrease of HSC number in BM, suggesting that endothelial cells play indispensable roles for HSC maintenance through producing these niche factors [12].

Endothelial cells have also been shown to regulate HSC quiescence through surface molecule E-selectin expression. Deletion or blockade of E-selectin promoted HSC quiescence and increased survival through undefined mechanism [13].

Although the heterogeneity of endothelial cell populations remains largely unresolved, endothelial cells with a high expression of CD31 and endomucin (Emcn), referred to as type H endothelium, which are found in end-terminal arterioles connecting to sinusoids, expressed Kitl-encoding stem cell factor at higher levels than sinusoidal type L endothelial cells [14].

A differential role of endothelial cells is reflected by the difference of vascular permeability observed between sinusoids and arterioles which has repercussions on HSC egress and homing. Arterial vessels are less permeable and maintain HSCs in a low reactive oxygen species, keeping HSCs in a quiescent state. On the contrary, more leaky sinusoids expose HSCs to blood plasma and promote high level of ROS in HSCs, augmenting the ability of differentiation and migration [15].

Pericytes

Pericytes have long projections that surround the blood vessel wall in almost all tissues [16]. They are defined by their anatomical locations in combination with several molecular markers such as platelet-derived growth factor receptor β, CD146, neuron-glial 2, SMA, 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 [17].

Interestingly, an evaluation of the cell cycle status demonstrated that arteriolar pericytes are largely quiescent. Tridimensional imaging of the adult mouse BM has revealed that the majority of dormant HSCs are located close to arterioles, and genetic depletion of arteriolar pericytes resulted in migration of HSCs away from the arterioles, switching them into nonquiescent status. This proposes that arteriolar pericytes promote HSC dormancy, essential for HSC maintenance in the BM [5]. Nevertheless, the molecular mechanisms by which arteriolar pericytes regulate HSC quiescence remain to be clearly defined.

Schwann cells

Schwann cells are the main glial cells of the peripheral nervous system. In the BM, they are present in their unmyelinated form associated with sympathetic and sensory nerve fibers [17]. 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 [18].

Schwann cells were shown to produce several cytokines and to express cytokine receptors as well [19]. Studies have suggested that BM Schwann cells regulate the hibernation and activation of HSCs. In a study, using immunohistochemistry, the expression of active transforming growth factor-beta (TGF-β) was suggested to be confined to BM Schwann cells. BM denervation reduced the number of cells producing active TGF-β, leading to a loss of HSCs from the BM [20].

However, denervation does not only affect Schwann cells; for instance, β-adrenergic signals from the sympathetic nervous system have been shown to regulate enforced and circadian HSC egress [21]. Moreover, in addition to Schwann cells, other cells, including megakaryocytes, produce TGF-β in the BM. TGF-β1 derived from megakaryocytes has been shown to maintain HSC quiescence. Most of BM innervation – and Schwann cell ensheathing of those nerve fibers – runs along arterioles in the BM [22].

As arterioles contain several cell types, the identity of the cell promoting HSC quiescence is still unknown. 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 secreted by those cells.

Nerves

Signals from the sympathetic nervous system have been identified as regulatory components of the HSC niche [23]. Sympathetic nerves secrete catecholamines, which are delivered to the BM microenvironment by the blood circulation or by secretion from the nerve endings acting in paracrine signaling [24].

It has been shown that trafficking of HSCs into the bloodstream during steady state is strongly regulated through the circadian release of adrenergic signals from the sympathetic nerves in the BM [17].

Adrenergic signaling reduces CXCL12 expression in the BM [25]. Moreover, 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. Induction of sympathetic neuropathy by malignant cells has been demonstrated [26].

HSCs express catecholaminergic receptors, suggesting that they are able to directly respond to signals from the sympathetic nervous system. Treatment of HSCs with dopamine agonists augments colony-formation *in vitro*, albeit only in the presence of granulocyte-colony stimulating factor (G-CSF). Pretreatment of HSCs with dopamine agonists augments their ability to engraft. Additionally, norepinephrine treatment of HSCs also enhances both colony-formation capabilities *in vitro* and engraftment *in vivo* [27].

Additionally, the sympathetic nervous system adjacent to the dorsal aorta plays a vital role in HSC specification during development [28].

Osteoclasts

Osteoclasts 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, which enhances mobilization [29].

On the contrary, 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. Bone resorption also produces active TGF-β, which can act on HSCs [30]. Osteoclast inhibition by bisphosphonates causes a reduction in the number of HSCs and delays hematopoietic recovery. Using a mouse model with loss of osteoclast activity, osteoclasts have been shown to regulate mesenchymal cell differentiation and HSC maintenance [31].

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 [32].

Radio-resistant macrophages protect the HSC pool from exhaustion by producing prostaglandin E2 after irradiation [33]. BM-resident macrophages are defined based on differential expression of numerous molecular markers, such as Gr-1, F4/80, CD115, and CD169 [34].

Their numbers are reduced during G-CSF-induced HSC mobilization, and following their loss, HSCs egress to the peripheral circulation [30]. Additionally, a separate subpopulation of macrophages expressing high levels of smooth muscle actin and cyclooxygenase 2 was recently identified. This rare macrophage population synthesizes prostaglandin E2, which increases CXCL12 expression in nestin-GFP (Green Fluorescent Protein)+mesenchymal stem cells [35] and CXCR4 expression on HSCs, 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 [36].

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. Subsequent studies have suggested that this factor is oncostatin M [37].

Thus, macrophages and sympathetic nerves exert the opposite action to the microenvironment, forming a regulatory loop. HSC retention in the BM and the spleen relies at least partially on a ligand for vascular cell adhesion molecule 1, integrin VLA-4 [38], which is expressed by macrophages. A subsequent study described that macrophages are important players in splenic HSC retention, as depleting macrophages using inducible diphtheria toxin receptor expression at the CD169 locus or silencing VCAM-1 in macrophages caused release of HSCs from the spleen.

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 [39].

It had been shown that neuropeptide Y deficiency impairs HSC survival and BM regeneration. Furthermore, pharmacological elevation of neuropeptide Y prevented the deficits, whereas neuropeptide Y injection into mice lacking the Y1 receptor specifically in macrophages did not rescue BM dysfunction [40].

Macrophage depletion also delays erythropoietic recovery following acute blood loss, myelo-ablation, or challenge with hemoglobin-oxidizing phenylhydrazine. Interestingly, polycythemia vera, which is characterized by increased 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 JAK2V617F mutation. These studies suggest that macrophages are crucial 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 are thought to be very large, express F4/80, and do not express Mac1 [41]; 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 promoting the maintenance and retention of HSCs.

Megakaryocytes

A subset of HSCs is located near megakaryocytes in the BM [42].

Megakaryocytes produce multiple cytokines (e.g. thrombopoietin, TGF-β, 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 ~20% of HSCs in the BM. Megakaryocytes serve as HSC-derived niche cells directly regulating HSC function [43].

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 to promote HSC engraftment and hematopoietic reconstitution after BM transplantation [44].

The migration of megakaryocytes to the endosteum is thought to depend on thrombopoietin signaling, as the inhibition of c-Mpl reduces megakaryocyte migration after radioablative conditioning. More findings have identified a direct HSC regulation by megakaryocytes in steady-state hematopoiesis. Ablation of megakaryocytes reduces HSC engraftment and proliferation [44].

Thrombopoietin administration to megakaryocyte-depleted mice restores the number of quiescent HSCs [42], suggesting that thrombopoietin may contribute to regulation of HSCs by megakaryocytes.

Megakaryocytes secrete high levels of TGF-β, which regulates HSCs. Conditional deletion of TGF-β1 in megakaryocytes increases HSC activation and proliferation in young mice. In addition, TGF-β injection into megakaryocyte-depleted mice restores HSC quiescence [45].

Under homeostatic conditions, megakaryocytes maintain HSC quiescence through TGF-β signaling, whereas under stress, megakaryocytes promote HSC expansion via fibroblast growth factor 1 production. CXCL4, which is produced by megakaryocytes, negatively regulates HSC proliferation, reduces HSCs numbers, and decreases engraftment. An increase in HSC number, proliferation, and repopulating activity was observed in CXCL4 knockout mice [46].

Lymphocytes

Lymphocytes, essential for both cell-mediated and antibody-mediated immunity, are broadly distributed throughout the BM parenchyma and make up a major fraction of total BM mononuclear cells [47]. Lymphocytes have been suggested to influence hematopoiesis, potentially through direct cellular interactions with the HSCs. Natural killer cells have been suggested to play a negative role in HSC differentiation [48].

Regulatory T cells make up one-third of all CD4+ T cells in the BM [49]. Depletion experiments and cotransfer of BM with regulatory T cells indicated that these cells suppress colony formation and myeloid differentiation of HSCs [50].

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. However, whether this interaction is biologically relevant to homeostatic HSCs maintenance is still unclear. Furthermore, regulatory T cells have been suggested

to provide an immune-privileged microenvironment in the BM, protecting HSCs from immune attacks [51].

Neutrophils

Neutrophils are the most abundant subpopulation of leukocytes. Neutrophils have a short circulating half-life (6–8 h), after which they quickly migrate to tissues where they perform their functions [52].

Serine proteases derived from neutrophils are capable of cleaving several cytokines and receptors essential for HSCs retention *in vitro*, including CXCL12, CXCR4, VCAM-1, c-Kit, and SCF, suggesting that activated neutrophils create a proteolytic niche that may contribute to HSCs release from the BM. However, it was shown that, in mice lacking these proteases, G-CSF-induced HSC mobilization proceeds normally [53], suggesting that serine proteases are not essential for BM egress. G-CSF induces neutrophil expansion in the BM, which may lead to mesenchymal stem cell and osteoblast apoptosis and reductions in the expression of factors that are responsible for HSC retention in the BM. However, neutrophil number in the BM does not certainly correlate with HSCs mobilization [54].

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 [55]. 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 explain how the daily clearance of aged neutrophils in the BM generates signals that affect HSCs in the BM niches [36].

Conclusion

In the homeostasis state, niche precisely controls the HSC fate decisions and adjusts a balance between the rate of HSC self-renewal and differentiation. Mobilization and homing of HSCs are important physiological processes and are highly controlled by niche elements.

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Conflicts of interest

There are no conflicts of interest

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