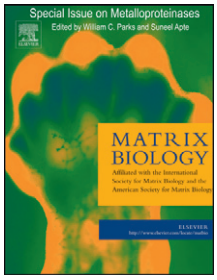
Review



Matrix metalloproteinases in stem cell mobilization

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Abstract

Hematopoietic stem cells (HSCs) have the capability to migrate back and forth between their preferred microenvironment in bone marrow niches and the peripheral blood, but under steady-state conditions only a marginal number of stem cells can be found in the circulation. Different mobilizing agents, however, which create a highly proteolytic milieu in the bone marrow, can drastically increase the number of circulating HSCs. Among other proteases secreted and membrane-bound matrix metalloproteinases (MMPs) are known to be involved in the induced mobilization process and can digest niche-specific extracellular matrix components and cytokines responsible for stem cell retention to the niches. Iatrogenic stem cell mobilization and stem cell homing to their niches are clinically employed on a routine basis, although the exact mechanisms of both processes are still not fully understood. In this review we provide an overview on the various roles of MMPs in the induced release of HSCs from the bone marrow.

The Hematopoietic Stem Cell Niches

The last decade has witnessed an enormous increase in the knowledge pertaining to the hematopoietic stem cell microenvironment in the bone marrow. More than 35 years ago, the British hematologist Raymond Schofield coined the term 'stem cell niche' [1], but it took more than 25 years to prove the concept of a specific cellular and molecular microenvironment in the bone marrow [2,3] which can maintain stem cells while controlling their differentiation into lymphoid and myeloid progenitor cells and hence, giving rise to all blood cells. Today, two major types of niches essential for HSC maintenance, an endosteal niche and vascular niches, have been identified and characterized, mainly in the murine bone marrow [4–6]. However, it is still an unsettled issue as to which niche harbors the quiescent long-term repopulating hematopoietic stem cell(s).

The cellular composition of the niches is quite complex. Key cell types in the endosteal niche are the bone-lining osteoblasts, which can develop from mesenchymal stromal/stem cells (MSCs). Phagocytic cells can support the maintenance of both osteoblasts and MSCs [7,8]. $CD45^{-}CD105^{+}$ murine osteoprogenitor cells, when transplanted under the kidney capsule, are able to rebuild a hematopoietic stem cell niche [9]. Similarly, human bone marrow-derived $CD146^{+}$ MSCs are capable, upon transplantation, of transferring a hematopoietic stem cell microenvironment to heterotopic sites [10]. Not only the osteoprogenitor cells, but also the highly proteolytically active osteoclasts have been implicated in playing a role in the endosteal niche [11]. On the other hand, endothelial cells of the sinusoids or arterioles are ensheathed with $nestin^{+}$ and $leptin\text{-}receptor^{+}$ MSCs, respectively, which are the major cell types in the vascular niches [12,13]. The relationship of these MSC subtypes to the CXCL12-abundant reticular

(CAR) cells is still an unresolved issue [14,15]. Sympathetic nerves which are found to localize close to nestin$^+$ MSCs can regulate MSC proliferation, suppression of osteoblast function and the circadian oscillation of HSC retention factors [16,17]. While the aforementioned cell types mainly support the maintenance of the HSCs, adipocytes within the bone marrow have been identified as negative regulators of hematopoiesis [18].

The second essential constituents of the niches are biochemical and biophysical signals provided by the different niche cells. The chemokine CXCL12 (also known as stromal cell-derived factor-1, SDF-1) which interacts with its receptor CXCR4 on hematopoietic stem and progenitor cells (HSPCs) is synthesized and secreted by various niche cells including CAR cells, nestin$^+$ and leptin-receptor$^+$ MSCs and osteoblasts [12,14,19]. CXCL12 plays a key role in the quiescence and retention of HSCs in the bone marrow [20]. However, targeted deletion of CXCL12 in the different niche cell types led to different outcomes indicating that not all sources of CXCL12 production are indispensable for HSC maintenance [21]. Membrane-bound and secreted stem cell factor (SCF), mainly expressed by endothelial cells and perivascular MSCs, is another important example of an essential player for HSC maintenance [13]. The cell adhesion molecules E-selectin and VCAM-1 expressed on bone marrow endothelial cells also have a strong influence on HSPC proliferation and self-renewal [22,23], while the hyaluronan receptor CD44 expressed on HSPCs regulates the retention of these cells to the bone marrow [24,25]. Besides these 'chemical' signals, biophysical parameters such as substrate elasticity, cell stiffness or cell shape strongly influence the properties of HSCs in their niches. Holst and coworkers provided strong evidence that mouse and human HSPCs in vitro can directly respond to biomechanical signals with an increased expansion of an undifferentiated stem cell population [26]. HSPCs are able to sense changes in the elasticity of niche cells mediated by signals from the sympathetic nervous system [17,27]. Contractility of HSPCs is required for their engraftment to the niches [28]. Finally, the topography of the niche can induce deformation of the cytoskeleton of niche cells with an influence on their differentiation [29].

The Extracellular Matrix of the Stem Cell Niches

The third essential component of the HSC niches is their secreted extracellular matrix (ECM) which is not only an anchoring substrate for HSCs, but can also direct the cell fate of the HSCs either by interacting with matrix receptors mainly of the integrin family, by mechano-transduction or by presentation of bioactive growth factors. In contrast to the well-studied cellular components of the HSC niches, functions of the ECM in these niches are still not very intensively analyzed. Different collagen types, tenascin-C, laminins, osteopontin, fibulins, perlecan and agrin are the most prominent components found in the bone marrow microenvironment. The fibrillar collagen type I is the most abundant collagen type in bone and a calcium-sensing receptor expressed on HSPCs can mediate binding to collagen I [30]. Other adhesive collagen types in the bone marrow are the microfibrillar collagen type VI and the fibril-associated collagen XIV [31,32]. The latter collagen types mainly interact with myeloid and lymphoid cell types, but whether they are also involved in the retention of the early HSPCs in the niches is not known so far. Tenascin-C is an adhesive and proliferation-enhancing factor for HSPCs [33–35]. Mice lacking tenascin-C showed a normal white blood cell count both in the periphery and in the bone marrow, however, the number of colony-forming units representing different hematopoietic progenitor cells was markedly reduced in these animals [36]. Upon myeloablation of normal mice with sublethal irradiation, a strong up-regulation of tenascin-C was found in CAR cells [37]. HSPCs bind to tenascin-C via the integrin α9β1 and antibodies against this integrin could inhibit HSPC proliferation and also adhesion to osteoblasts [38]. Osteopontin can also interact with the integrin α9β1, but this ECM component is a negative regulatory element of the hematopoietic stem cell pool [39–41]. Anti-adhesive substrates of the bone marrow include members of the fibulin family and the large proteoglycan perlecan [42,43]. Another proteoglycan with a niche-specific role is agrin which is expressed by MSCs and their descendants, the osteoblasts. HSPCs express the agrin receptor α-dystroglycan, and agrin$^+$ MSCs supported HSPC proliferation [44]. Finally, members of the laminin family containing the alpha4- or alpha5-chains are expressed by different niche cells. The sinusoidal cells deposit a laminin-rich basement membrane, but osteoblasts and bone marrow stromal cells can also express the alpha4- and alpha5-chain-containing isoforms although they do not deposit a structurally intact basement membrane [45–47]. The laminin isoforms containing the alpha5-chain are the strongest adhesive laminin substrate for HSPCs in the bone marrow niches, an interaction which is mainly mediated by the integrin α6β1 [46,47].

Stem Cell Mobilization and Mobilizing Agents

Bone marrow transplantation, i.e., transplantation of HSCs, is a well-established therapy during irradiation and/or chemotherapy in the course of cancer treatment. Currently, HSPCs are mostly collected from the