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REVIEW

Hematopoietic niches, erythropoiesis and anemia of chronic infection

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Anemia is a significant co-morbidity of chronic infections, as well as other inflammatory diseases. Anemia of chronic infection results from defective bone marrow erythropoiesis. Although the limitation of iron availability has been considered a key factor, the exact mechanisms underlying blockade in erythroid generation during infection are not fully understood. Erythropoiesis is a tightly regulated process that is very sensitive to environmental changes. During the last decade, the importance of the bone marrow hematopoietic niche has been progressively acknowledged. Several bone marrow cell types (such as macrophages, mesenchymal stem cells, and progenitor cells) and molecular mediators (such as CXCL12) have been identified as fundamental for both the maintenance of hematopoietic stem cell pluripotency and their most adequate differentiation into each hematopoietic cell lineage. Importantly, both niche-supporting cells and hematopoietic progenitors were found to be able to sense local and systemic cues to adapt the hematopoietic output to needs of the organism. Here, we review how hematopoietic progenitors and niche-supporting cells sense and respond to stress cues and suggest a potential role for the hematopoietic niche in the development of anemia of chronic infection.

Hematopoiesis is a critical biological process responsible for generation of not only different types of leukocytes, but also erythrocytes, which have the major task of delivering oxygen to peripheral tissues. All circulating blood cells are generated from hematopoietic stem cells (HSCs), which are maintained mainly in the bone marrow (BM) during adult life. To ensure continuous and controlled output of hematopoietic cells, some HSCs lose their quiescence and enter a highly regulated differentiation process. It has been increasingly acknowledged that participation of a HSC in a self-renewal or differentiation process is determined by micro-environmental signals [1–8]. This BM microenvironment or niche, in turn, senses and responds to the state and needs of different tissues of the organism.

In the last decade, research began to focus on the cellular constituents of the hematopoietic niche. Mesenchymal stem/progenitors cells (MSPCs), which are multipotent cells capable of differentiating into osteoblasts, chondrocytes, adipocytes, and stromal cells [9], produce factors, such as stem cell factor (SCF) and C–X–C motif ligand 12 (CXCL12), important for HSC self-renewal, survival, and retention in the niche [2,3,5–7,10–16]. Endothelial cells have also been reported to support multilineage hematopoietic differentiation in vitro [17–20]. Of note, deficiency in the interleukin (IL)-6 family cytokine receptor gp130 in bone marrow endothelial cells leads to severe anemia, which cannot be compensated by extramedullary erythropoiesis [21]. Despite early reports implying that osteoblasts participated in regulation of the HSC maintenance niche [22–26], it is currently accepted that osteoblasts do not directly regulate HSC, but support B lymphopoiesis [2,24,27–29]. $CD169^{+}$ macrophages also regulate the hematopoietic niche by cross-talking with MSPCs, inducing expression of the chemokine CXCL12 and, thus, promoting the retention of HSCs and progenitors in the hematopoietic niche [30]. Other mature hematopoietic cells also play a

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role in forming the hematopoietic niche. Megakaryocytes secrete the chemokine CXCL4, which controls HSC cell cycle activity [4]. $CD8^+$ cytotoxic T cells (CTL), a key component of the host defense against intracellular pathogens, secrete interferon γ (IFNγ), which acts on BM MSPCs, promoting their release of cytokines such as IL-6. The IL-6 produced by MSPCs causes an increase in myelopoiesis, through downregulation of the transcription factors Runx-1 and Cebpα in early hematopoietic progenitor cells [31]. These observations suggest that mature hematopoietic cells can influence early multipotent hematopoietic progenitors, modulating their differentiation into specific hematopoietic lineages, namely during an immunologic response. The results also imply that MSPCs are important constituents of the BM microenvironment/niche, acting as regulators of hematopoietic differentiation in response to local and peripheral environmental cues. During infection, this response is most probably based on the expression of cytokine and chemokine receptors. Apart from these, hormones can also impact hematopoiesis. HSCs express large amounts of estrogen receptor α, whose signaling promotes HSC self-renewal and erythropoiesis during pregnancy [32]. Additionally, central nervous system (CNS) signals can also modulate hematopoiesis. Sympathetic nerves enwrap MSPCs and secrete noradrenaline in a circadian manner, which is sensed by MSPCs, causing them to reduce expression of CXCL12 and, thus, enhancing the BM egress of HSCs and progenitors [33,34].

Despite recent efforts to gain an understanding of the cellular and molecular components of the HSC maintenance niche, there remains a gap in the understanding of how the niche directs and supports differentiation into specific lineages, especially during stress responses such as infection.

Bone marrow erythropoiesis

In mammals, erythropoiesis occurs mostly in BM during adult life and proceeds through highly controlled sequential stages of differentiation from HSCs to mature red blood cells (RBCs) (Fig. 1). The transcription factor PU.1 is critical to the specific lineages into which the HSCs differentiate. In erythropoiesis, PU.1 is required for the in vitro self-renewal of erythroblasts, and PU.1-deficient erythroblasts differentiate prematurely [35].

Hematopoietic stem cells, as well as megakaryocytic and erythroid progenitors, depend on maintenance of stromal cells in place through integrin-mediated adhesion and cytokines directing them to undergo erythroid differentiation [36]. HSCs and the first erythroid lineage-committed progenitors, burst-forming unit–erythroid (BFU-E) cells, are dependent on SCF (produced most likely by MSPCs), whose ligand is cKIT. SCF is needed for the survival and proliferation of early erythroid progenitors and precursors up to the colony-forming unit–erythroid (CFU-E) stage. By preventing further erythroid differentiation and maturation, SCF signaling ensures self-renewal of the erythroid progenitor pool. cKIT is highly expressed in BFU-E and CFU-E, but downregulated at later stages of CFU-E differentiation. It is not expressed by polychromatic and orthochromatic erythroblasts, suggesting that the later stages of erythrocyte differentiation are mostly independent of SCF, but critically dependent on erythropoietin (Epo). Epo signals erythropoiesis in vivo by suppressing non-erythroid lineage potential, inducing an erythroid lineage bias in early hematopoietic progenitors, increasing erythropoiesis, and decreasing myelopoiesis [37]. Thus, Epo is an example of a systemically released cytokine that regulates lineage choices in multipotent hematopoietic cells present in the bone marrow. Epo is produced by cortical interstitial cells adjacent to the proximal tubules in the kidney, and is responsible for maintaining the homeostasis of circulating erythrocyte numbers. The systemic concentrations of Epo are normally low, but small decreases in hematocrit result in exponential increases in serum concentrations of the cytokine. Epo and SCF act in synergy to induce the proliferation of pro-erythroblasts (Pro-E), which differentiate into erythroblasts [38]. Erythroblasts, in turn, surround BM macrophages, forming erythroblastic islands dispersed throughout the BM. Within these erythroblastic islands, erythroblasts proliferate, differentiate, and enucleate, giving rise to anucleated reticulocytes [39,40]. $CD169^+$ macrophages are a key component of erythroblastic islands, supporting late erythroid maturation [41]. They are thought to be involved in providing iron to erythroblasts to be used in

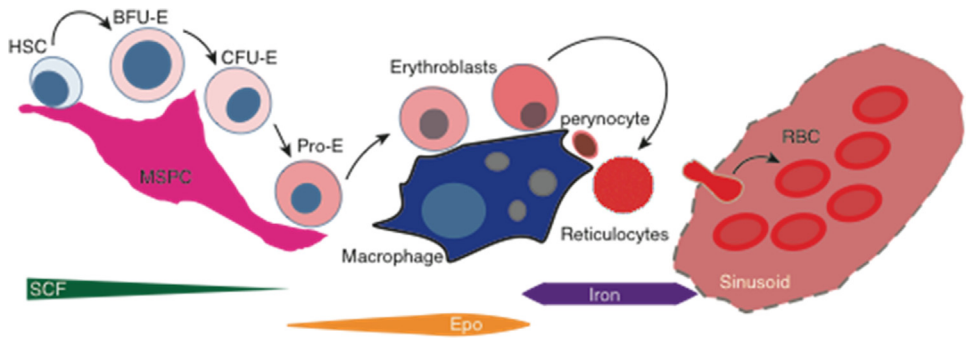

Figure 1. Differentiation of HSCs into mature erythrocytes. The most important factors involved in specific developmental stages are depicted.