Ioannis Mitroulis, Lydia Kalafati, George Hajishengallis, Triantafyllos Chavakis

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Myelopoiesis in the Context of Innate Immunity

Ioannis Mitroulis[a, b] Lydia Kalafati[a–c] George Hajishengallis[d]
Triantafyllos Chavakis[a]

[a]Institute for Clinical Chemistry and Laboratory Medicine, Technische Universität Dresden, Dresden, Germany; [b]National Center for Tumor Diseases, Dresden, Germany; [c]German Cancer Research Center (DKFZ), Heidelberg, Germany; [d]University of Pennsylvania, Penn Dental Medicine, Department of Microbiology, Philadelphia, PA, USA

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Abstract
An intact and fully functional innate immune system is critical in the defense against pathogens. Indeed, during systemic infection, the ability of the organism to cope with the increased demand for phagocytes depends heavily on sufficient replenishment of mature myeloid cells. This process, designated emergency or demand-adapted myelopoiesis, requires the activation of hematopoietic progenitors in the bone marrow (BM), resulting in their proliferation and differentiation toward the myeloid lineage. Failure of BM progenitors to adapt to the enhanced need for mature cells in the periphery can be life-threatening, as indicated by the detrimental effect of chemotherapy-induced myelosuppression on the outcome of systemic infection. Recent advances demonstrate an important role of not only committed myeloid progenitors but also of hematopoietic stem cells (HSCs) in emergency myelopoiesis. In this regard, pathogen-derived products (e.g., Toll-like receptor ligands) activate HSC differentiation towards the myeloid lineage, either directly or indirectly, by inducing the production of inflammatory mediators (e.g., cytokines and growth factors) by hematopoietic and nonhematopoietic cell populations. The inflammatory mediators driving demand-adapted myelopoiesis target not only HSCs but also HSC-supportive cell populations, collectively known as the HSC niche, the microenvironment where HSCs reside. In this review, we discuss recent findings that have further elucidated the mechanisms that drive emergency myelopoiesis, focusing on the interactions of HSCs with their BM microenvironment.

Introduction

The innate immune system is the first line of host defense against pathogens. Several cell populations and soluble factors act in concert to restrict pathogens and prevent systemic infection. Innate immune cell mobilization from the bone marrow (BM), especially the mobilization of neutrophils, and their accumulation at the site of infection are crucial in containing the pathogen [1]. In the course of severe systemic infection, the acute demand for vast numbers of neutrophils to cope with the infection renders the constant replenishment of circulating neutro-

E-Mail karger@karger.com
www.karger.com/jin

Dr. Ioannis Mitroulis
Technische Universität Dresden
Fetscherstrasse 74
DE–01307 Dresden (Germany)
E-Mail ioannis.mitroulis@uniklinikum-dresden.de

phils from the BM imperative. This process, termed emergency or demand-adapted myelopoiesis, is mediated by the activation of hematopoietic stem cells (HSCs) and progenitor cells in the BM [2]. In this review, we discuss the contribution of hematopoietic progenitor cell populations to the innate immune response.

HSCs and Hematopoietic Hierarchy

HSCs, at the top of the hematopoietic hierarchy, are quiescent cells with multipotent and extensive self-renewal potential, and reside in the BM niche [3]. HSC maintenance in the BM niche and their activation status is regulated by cell-intrinsic factors including transcriptionally regulated programs and cellular metabolism, as well as by the components of the niche micro-environment [4].

HSC differentiation to multipotent progenitor (MPP) cells is the initial step in a cascade of events resulting in mature hematopoietic cells, including cells of innate immunity, although tissue-resident macrophages may derive from embryonic progenitors [5, 6]. MPPs show higher proliferation rates than HSCs, and are therefore considered to play a major role in the maintenance of unperturbed hematopoiesis, but the exact contribution of HSCs to steady-state hematopoiesis is under debate [7–9]. MPPs subsequently give rise to progenitor cells with myeloid lineage commitment (common myeloid progenitors; CMPs) or lymphoid lineage commitment (common lymphoid progenitors; CLPs) [3]. There is an imbalance between the myeloid and lymphoid output of MPPs, since differentiation to CMPs has been shown to be substantially higher than differentiation to CLPs [7]. Further steps of differentiation of CMPs toward more restricted progenitors, e.g., granulocyte-macrophage progenitors (GMPs), erythrocyte-megakaryocyte progenitors, and monocyte-dendritic cell progenitors, and, as a next stage, toward restricted granulocyte progenitors, monocyte progenitors, and common dendritic progenitors, result in a huge amplification of innate immune cell production, generating an adequate number of neutrophil cells [10, 11].

The hierarchical model of hematopoiesis is, however, oversimplified, given the high heterogeneity of hematopoietic and myeloid progenitor cell populations [12, 13]. A typical example is the characterization of an HSC subpopulation that expresses CD41, which shows lineage bias toward myelopoiesis [14]. Similarly, MPPs can be divided into subpopulations with increased myeloid or lymphoid bias based on the expression of the receptor tyrosine kinase Flt3 [15, 16]. Recent studies, using single-cell analysis approaches and genetic labeling, have further demonstrated high heterogeneity in progenitor cell populations, and, importantly, that lineage commitment decisions may be taken earlier, at the level of primitive HSCs [17–19]. For example, it has been recently shown that at steady-state hematopoiesis, megakaryocyte-erythroid lineage derives from early HSCs, while certain HSC clones display a restricted output of myeloid lineage cells [17]. Single-cell transcriptomic analysis revealed a correlation between the myelopoiesis-related gene signature and signatures associated with cell cycle and proliferation, further underlining the increased necessity for myeloid cell production in the BM when compared to lymphocytes [19]. These findings challenge the long-standing perception that lineage specification takes place at the level of the bifurcation into CMPs and CLPs.

Emergency Myelopoiesis

The production of innate immune cells, especially neutrophils, is a major task that the hematopoietic system needs to fulfill under steady-state conditions, as the estimated daily production of neutrophils in adult humans is $0.5–1 \times 10^{11}$ [20]. The demand for neutrophil generation increases dramatically during hematopoietic stress induced by chemotherapy-associated myeloablation or systemic infection/inflammation. Administration of myeloablative regimens often results in profound neutropenia, which can lead to life-threatening infectious complications (febrile neutropenia) [21]. Systemic infection or inflammation is characterized by increased neutrophil numbers (neutrophilia) and the presence of myeloid precursor cells ("left shift") in peripheral blood. This enhanced demand for the generation and release of neutrophils from the BM to peripheral blood upon systemic infection/inflammation derives from the accumulation of vast numbers of neutrophils and subsequent neutrophil cell death at the sites of pathogen invasion or inflammation [22].

Replenishment of the neutrophil pool after myeloablation or systemic infection requires the activation of dormant HSCs, and a switch from a quiescent to a proliferative state [4]. In this context, several cytokines, growth factors, and pathogen-derived products, e.g., Toll-like receptor (TLR) ligands, including bacterial lipopolysaccharide (LPS) or lipoproteins, may activate HSCs, thereby changing their transcriptional program [4]. This activa-

tion of hematopoietic progenitors leads to an increased production of GMPs, which then expand in numbers, form clusters, and further differentiate towards neutrophils [23], facilitating emergency myelopoiesis. In the same context, a recent study demonstrated that committed neutrophil precursors proliferate and expand upon systemic infection or tumoral stress, giving rise to immature neutrophils that migrate to peripheral tissues [24].

Myeloid Growth Factors and Cytokines

Systemic infection/inflammation leads to a strong increase in the levels of growth factors that promote myelopoiesis [25, 26]. Granulocyte colony-stimulating factor (G-CSF) is critical for basal neutrophil production, as shown by the reduced numbers of circulating neutrophils in mice deficient in G-CSF (*Csf3*$^{-/-}$) or its cognate receptor (*Csf3r*$^{-/-}$) [27, 28]. Moreover, G-CSF-deficient mice display decreased numbers of granulocyte precursors and defective neutrophil mobilization [27]. G-CSF acts directly on CMPs and GMPs, instructing them toward granulopoiesis [29, 30], but in the case of HSCs, it regulates the cell cycle [31] and drives their mobilization in an indirect fashion, by affecting the BM microenvironment [32, 33]. During systemic inflammation, endothelial cells, rather than cells of hematopoietic origin like resident macrophages, are the main cellular source of G-CSF by responding to LPS through TLR4, as demonstrated by BM chimera experiments [34, 35]. In murine models of infection with different microbes, alongside G-CSF, granulocyte-macrophage (GM)-CSF has been implicated in emergency myelopoiesis, and G-CSF- and GM-CSF-independent pathways of neutrophil generation in emergency myelopoiesis have been described upon infection with *Candida albicans* [36, 37]. The ability of G-CSF to promote HSC proliferation and drive myelopoiesis is therapeutically important. Indeed, prophylactic administration of G-CSF is currently recommended for patients at an increased risk of developing febrile neutropenia [38, 39].

Macrophage colony-stimulating factor (M-CSF) acts also directly on HSCs, driving them toward myelopoiesis [40, 41]. M-CSF has been shown to activate PU.1, a master regulator of myelopoiesis, instructing myeloid lineage decision [40]. In addition, GM-CSF activates hematopoietic progenitors toward myelopoiesis [42, 43]. Although GM-CSF deficiency does not alter hematopoietic progenitor cell numbers under steady state, GM-CSF contributes to emergency myelopoiesis in response to infection with *Mycobacterium avium* [36]. Blocking of GM-CSF was further shown to impair the expansion of hematopoietic progenitors in the context of β-glucan-induced trained immunity [44].

Several studies have focused on the role of cytokines produced during systemic inflammation [45] for the activation of hematopoietic progenitor cells in emergency myelopoiesis. IL-1β directly activates hematopoietic progenitor cells, inducing cell cycle and myeloid bias [44, 46, 47]. Weisser et al. [46] demonstrated that HSCs from mice with X-linked chronic granulomatous disease had increased cell proliferation, which was associated with defective repopulation potential and faster functional decline. Increased numbers of myeloid progenitors are also present in these mice, a finding indicative of myeloid-biased hematopoiesis. Blocking of IL-1 with the IL-1 receptor antagonist, anakinra, partially reversed the changes in hematopoietic progenitors, providing evidence that IL-1 participates in the detrimental effect of chronic inflammation on HSC function in this model.

IL-1 has been found to increase the proliferation and differentiation rate of HSCs in vitro, without having a similar effect on less primitive hematopoietic progenitors [47]. This effect was associated with induction in HSCs of the transcription factor PU.1 and the receptors of the myeloid-lineage growth factors GM-CSF (*Csf2ra*) and M-CSF (*Csf1r*), which are regulated by PU.1. The same study also demonstrated that chronic IL-1 administration impairs HSC self-renewal potential and drives myeloid differentiation, whereas acute IL-1 production in the BM supports reconstitution of myelopoiesis upon myelosuppression.

IL-6 contributes to the response of hematopoietic progenitors to emergency myelopoiesis after myeloablation. IL-6-deficient mice show an attenuated hematopoietic response to myeloablation after cytotoxic treatment [48], whereas administering IL-6 promotes the recovery of hematopoiesis after irradiation [49]. IL-27, a member of the IL-6/IL-12 family of cytokines, acts on hematopoietic progenitors in vitro, instructing them towards the myeloid lineage. Overexpression of IL-27 in mice was shown to promote myelopoiesis and suppress lymphopoiesis [50]. The role of this cytokine during emergency myelopoiesis was further confirmed in a model of malaria infection. As assessed by BM chimeras, ablation of the IL-27 receptor subunit WSX-1 in hematopoietic progenitors attenuated their expansion and their differentiation toward myeloid lineage, with significant consequences for the degree of parasitemia [51].

Interferon (IFN)-γ, a type II IFN that plays a critical role in host defense against pathogens, may impair the self-renewal capacity of HSCs [52–55]. Chronic myco-

bacterial infection promotes the differentiation of HSCs, leading to the attenuation of their repopulation capacity; this has been attributed to IFN-γ, as shown by studies using mice lacking the ligand-binding chain of the IFN-γ receptor (*Ifngr1*$^{-/-}$) [55, 56]. The role of IFN-γ in the response of HSCs to mycobacterial infection, as well as to myeloablation induced by chemotherapy, was further reinforced by a study that assessed the involvement of the interferon-inducible GTPase Lrg-47 (*Irgm1*) in HSCs. *Irgm1*$^{-/-}$ mice showed impaired expansion of hematopoietic progenitors in response to myeloablation induced by 5-fluorouracil and infection with *M. avium* [57].

Direct HSC Activation by Pathogen-Associated Molecules

Pathogen-associated molecular patterns (PAMPs) can directly activate HSCs through pattern recognition receptors, especially TLRs. HSCs express several TLRs [58]. In vitro activation of murine HSCs with TLR4 or TLR2 ligands, LPS, or Pam3CSK4 lipopeptide, respectively, promotes cell proliferation and differentiation into myeloid lineage in a myeloid differentiation primary response 88 (MyD88)-dependent manner [58].

Several groups have further tested the in vivo effect of TLR activation in hematopoietic progenitors. High-dose LPS administration results in pancytopenia by inducing cell death in BM cells and HSC dysfunction [59], whereas chronic in vivo administration of low-dose LPS over a period of up to 6 weeks results in the deterioration of the self-renewal and repopulating capacity of HSCs [60]. A recent study further demonstrated that LPS induces replication stress in HSC and impairs their repopulation capacity, in a pathway that involves reactive oxygen species (ROS), p38 mitogen-activated protein kinase (MAPK) and TRIF, but not MyD88 [61]. Interestingly, β-glucan-induced trained immunity may reverse the LPS-associated replication stress in HSCs, thereby pointing to a protective mechanism by which trained immunity may promote myelopoiesis [44]. Rodriguez et al. [62] have shown that severe sepsis, induced by *Pseudomonas aeruginosa* or the administration of its LPS, blocks HSC differentiation toward myeloid lineage, resulting in neutropenia. The same group further demonstrated in the same model that the TLR4-TRIF pathway impairs HSC and MPP function, whereas the TLR4-MyD88 pathway mainly affects myeloid lineage-committed cells [63]. Another study demonstrated that circulating HSCs can be recruited to sites of infection, where they generate tissue-resident myeloid cells in response to TLR activation [64]. Taken together, PAMPs can directly act on HSCs and induce their proliferation to myeloid lineage cells, a process that aims at promoting the replenishment of innate immune cells.

Regulation of Myelopoiesis by Transcription Factors

The differentiation of progenitors to mature granulocytes is tightly regulated by transcription factors, including PU.1, GF1, CCAAT-enhancer binding protein-α (C/EBPα), and C/EBPε [22]. PU.1 is critical for the differentiation of HSCs toward the myeloid lineage in response to M-CSF [40] or IL-1β [47]. C/EBPα is also important for the progression of granulopoiesis, mainly by regulating the expression of the G-CSF receptor [22]. A recent study has further evaluated the expression and role of these transcription factors during the late stages of granulopoiesis [24]. *Cebpa* expression was increased in GMPs compared to neutrophil precursors as well as immature and mature neutrophils, whereas *Cebpe* was necessary for the development of neutrophil precursors and was highly expressed in this cell population [24]. In addition, it was shown that mature neutrophils express higher levels of *Cebpd* than their precursors [24].

The HSC Niche in Emergency Myelopoiesis

Several nonhematopoietic and hematopoietic cell populations form a specialized microenvironment required for the maintenance of HSCs, designated the HSC niche [65]. Imaging of the BM reveals the perivascular localization of HSCs, even though the reports regarding their distribution in the perisinusoidal or periarteriolar region are conflicting [66, 67]. Perivascular mesenchymal stromal cells (MSCs) are critical players in the formation of the niche, by producing factors that support HSC maintenance [65]. In addition, sympathetic nerves, nonmyelinating Schwann cells, megakaryocytes, macrophages, and osteoclasts contribute to HSC niche formation [65, 68]. On the other hand, osteolineage cells support the reconstitution of hematopoiesis after HSC transplantation into irradiated recipient mice [65].

These cell populations regulate HSC function via cell-adhesive interactions and the release of soluble factors, like C-X-C motif chemokine ligand (CXCL)12, transforming growth factor (TGF)β1 or stem cell factor [69]. CXCL12 is produced in the BM microenvironment by several cell populations, including perivascular MSCs, and especially CXCL12-abundant reticular (CAR) cells [70], endothelial cells [71], and osteoblasts, although the contribution of CXCL12 produced by osteoblasts in the regulation of HSCs is controversial [69, 70]. In a similar

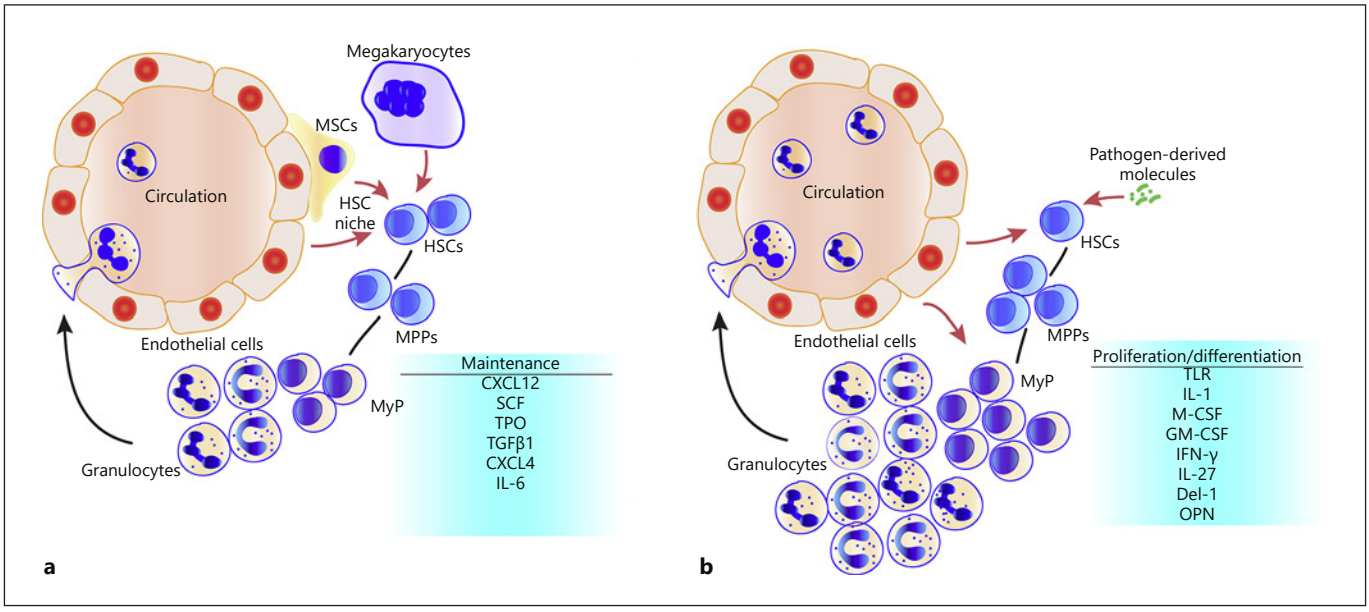

Fig. 1. Regulation of myelopoiesis in the hematopoietic stem cell (HSC) niche. **a** HSCs remain quiescent and are responsible for the maintenance of hematopoiesis. **b** Myeloablation or systemic inflammation drives HSC activation and differentiation to myeloid progenitors, to restore myelopoiesis. This balance between steady state and activation of HSCs depends on interactions with HSC niche, formed by mesenchymal stem cells (MSCs), endothelial cells, megakaryocytes, and macrophages. Factors that mediate HSC maintenance or proliferation/differentiation are listed. CXCL, C-X-C motif chemokine ligand; SCF, stem cell factor; TPO, thrombopoietin; TGF, transforming growth factor; IL, interleukin; TLR, Toll-like receptor; IFN, interferon; M-CSF, macrophage colony-stimulating factor; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; Del-1, developmental endothelial locus-1; OPN, osteopontin; MyP, myeloid progenitor.

fashion, stem cell factor, released by MSCs and endothelial cells [72], and thrombopoietin [73] support HSC maintenance. Inflammatory stimuli suppress the expression of these retention molecules in the HSC niche, driving the activation and differentiation of HSCs [74]. For example, G-CSF downregulates CXCL12 expression in the BM, thereby inhibiting HSC retention [75].

Recent studies demonstrated that megakaryocytes play an important role in the maintenance of HSCs in the quiescent state, via the release of CXCL4 and TGFβ1 [68, 76]. Moreover, megakaryocytes promote HSC proliferation by producing fibroblast growth factor (FGF)-1 in response to chemotherapy-induced myeloablation [76]. Resident macrophages play an important role in the BM microenvironment by regulating HSC niche via the clearance of aged neutrophils [77].

Besides releasing important soluble factors, endothelial cells regulate HSC trafficking, which takes place specifically at sinusoids due to increased vascular permeability. The increased permeability in sinusoids, compared to arterioles, was further associated with significantly increased levels of intracellular ROS in HSCs residing at the perisinusoidal region [71]. Since ROS promote the differentiation of HSCs [78], this finding suggests that the decreased permeability of arterioles may contribute to the increased quiescence of HSCs residing in the periarteriolar area. Consistently, endothelial cell-specific deletion of FGF receptor (Fgfr)-1 and -2 results in the disruption of vascular integrity, leading to increased levels of ROS in HSCs and a bias toward myeloid lineage after transplantation [71].

Cell-to-cell and cell-to-extracellular matrix interactions regulate HSC trafficking, retention, and quiescence in the BM microenvironment. E-selectin expressed in BM endothelial cells drives the proliferation of HSCs, affecting their response to chemotherapy [79]. Integrins expressed in HSCs play a major role in the adhesive interaction between HSCs and cells that form the HSC niche. For example, α4β1 integrin on HSCs contributes critically to the engraftment and mobilization of HSCs [80, 81]. Integrins of the β3 family also influence HSC function. For instance, intracellular signaling downstream of β3 integrin ligation regulates the effect of other factors like thrombopoietin and IFN-γ [54, 82]. In the same context, we have

recently shown that developmental endothelial locus (Del)-1, a protein produced in the BM by CAR cells and the endothelium, regulates HSC function by acting as a ligand of β3 integrin [83]. Del-1 deficiency impairs the regeneration of myelopoiesis after transplantation or LPS-induced systemic inflammation [83]. Additionally, competitive repopulation assays using donor cells from mice deficient in Del-1 [83] or mice with Del-1 overexpression in the endothelium [84], revealed a role for Del-1 in priming HSCs toward a myeloid lineage. Another protein expressed by BM stroma cells is osteopontin (OPN), which also regulates HSC function, albeit through α9β1 integrin [85, 86]. Decreased levels of OPN in aged BM have been recently associated with the myeloid skewing typically observed in aging [85], while OPN suppresses myelopoiesis in favor of lymphopoiesis during systemic fungal infection [87]. Distinct OPN isoforms may exert different actions; whereas the intracellular isoform is responsible for the impaired expansion of myeloid progenitors, the secreted isoform drives the expansion of CLPs [87]. Therefore, the interplay between HSCs, cell populations forming the niche, and locally produced soluble factors regulates the balance between HSC quiescence (Fig. 1a) and differentiation-associated proliferation (Fig. 1b).

Conclusion

Hematopoietic progenitors are a critical component of innate immunity, enabling the replenishment of innate immune populations in emergency myelopoiesis in the context of systemic infection or after chemotherapy-induced myelosuppression. Emergency myelopoiesis is a tightly regulated process involving contributions by several inflammatory mediators and HSC niche factors that typically tilt the hematopoiesis balance toward a myeloid lineage. The recently revealed molecular mechanisms provide promising molecular targets for the optimization of myelopoiesis in the context of disorders such as febrile neutropenia associated with chemotherapy.

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Disclosure Statement

The authors declare no conflicts of interest.

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