

REVIEW



# Regulation of myelopoiesis by proinflammatory cytokines in infectious diseases

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## Abstract

Hematopoiesis is hierarchically orchestrated by a very small population of hematopoietic stem cells (HSCs) that reside in the bone-marrow niche and are tightly regulated to maintain homeostatic blood production. HSCs are predominantly quiescent, but they enter the cell cycle in response to inflammatory signals evoked by severe systemic infection or injury. Thus, hematopoietic stem and progenitor cells (HSPCs) can be activated by pathogen recognition receptors and proinflammatory cytokines to induce emergency myelopoiesis during infection. This emergency myelopoiesis counterbalances the loss of cells and generates lineage-restricted hematopoietic progenitors, eventually replenishing mature myeloid cells to control the infection. Controlled generation of such signals effectively augments host defense, but dysregulated stimulation by these signals is harmful to HSPCs. Such hematopoietic failure often results in blood disorders including chronic inflammatory diseases and hematological malignancies. Recently, we found that interleukin (IL)-27, one of the IL-6/IL-12 family cytokines, has a unique ability to directly act on HSCs and promote their expansion and differentiation into myeloid progenitors. This process resulted in enhanced production of neutrophils by emergency myelopoiesis during the blood-stage mouse malaria infection. In this review, we summarize recent advances in the regulation of myelopoiesis by proinflammatory cytokines including type I and II interferons, IL-6, IL-27, granulocyte colony-stimulating factor, macrophage colony-stimulating factor, and IL-1 in infectious diseases.

**Keywords** Hematopoietic stem cell · Hematopoietic progenitor cell · Cytokine · Emergency myelopoiesis

## Abbreviations

BM	Bone marrow
CAR	C-X-C motif ligand 12-abundant reticular
CTL	Cytotoxic CD8 <sup>+</sup> T cell
CXCL	C-X-C motif ligand
DC	Dendritic cell
EC	Endothelial cell
G-CSF	Granulocyte colony-stimulating factor
gp130	β-Receptor glycoprotein 130

GM-CSF	Granulocyte macrophage colony-stimulating factor
HSC	Hematopoietic stem cell
HSPC	Hematopoietic stem and progenitor cell
IFN	Interferon
IFNAR	IFN-α receptor
IL	Interleukin
JAK	Janus kinase
LCMV	Lymphocytic choriomeningitis virus
LSK	Lineage <sup>-</sup> Sca-1 <sup>+</sup> c-Kit <sup>+</sup>
LT-HSC	Long-term repopulating hematopoietic stem cell
M-CSF	Macrophage colony-stimulating factor
MDSC	Myeloid-derived suppressor cell
MPP	Multipotent progenitor
MYD88	Myeloid differentiation primary response gene 88
MyRP	Myeloid-restricted progenitor cell
MSC	Mesenchymal stem/stromal cell
NK	Natural killer

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<i>P.</i>	<i>Plasmodium</i>
R	Receptor
RBC	Red blood cell
Sca-1	Stem cell antigen-1
SCF	Stem cell factor
STAT	Signal transducer and activator of transcription
Th	Helper T
TLR	Toll-like receptor
Treg	Regulatory T

## Introduction

### Hematopoietic stem cells

Blood cells must be continuously replaced because of their finite life span, and they are generated by the expansion and differentiation of a very small population of hematopoietic stem cells (HSCs) [1]. HSCs, therefore, have the dual capacity to self-renew and differentiate to generate all blood cell lineages. Self-renewal is the ability of HSCs to divide asymmetrically or symmetrically to produce one or two daughter stem cells that have a developmental potential similar to the mother cell. This ability is essential for HSCs to expand their numbers during development and maintain the proper HSC pool. HSCs also have an ability to differentiate. In this process, they lose their self-renewal capacity and generate various progenitor cells including multipotent progenitors (MPPs) and lineage-restricted progenitors that proliferate vigorously, resulting in the production of functional mature blood cells. Therefore, hematopoiesis is hierarchically organized, with the most immature and rare cell population, HSCs, located at the top of the hematopoietic hierarchy [2, 3]. Because frequent chromosomal replications generally increase the risk of oncogenic DNA mutations, HSCs are dormant and quiescent to maintain their genomic integrity and to avoid unnecessary proliferation and resultant exhaustion [4]. However, in response to various stimuli such as irradiation and cytotoxic chemotherapy, HSCs can replicate and proliferate. Moreover, because HSCs express receptors for cytokines and chemokines, as well as pattern recognition receptors such as Toll-like receptors (TLRs), HSCs can respond to signals from other cells and sense pathogens directly during infection or inflammation.

### Bone-marrow niche

The specialized microenvironment in the bone marrow (BM) that crucially regulates HSC dormancy, survival, and function through various soluble factors such as cytokines and cell contact-dependent interactions is called the BM niche. Various cell types including osteoblasts, perivascular cells, endothelial cells (ECs), mesenchymal stem/stromal

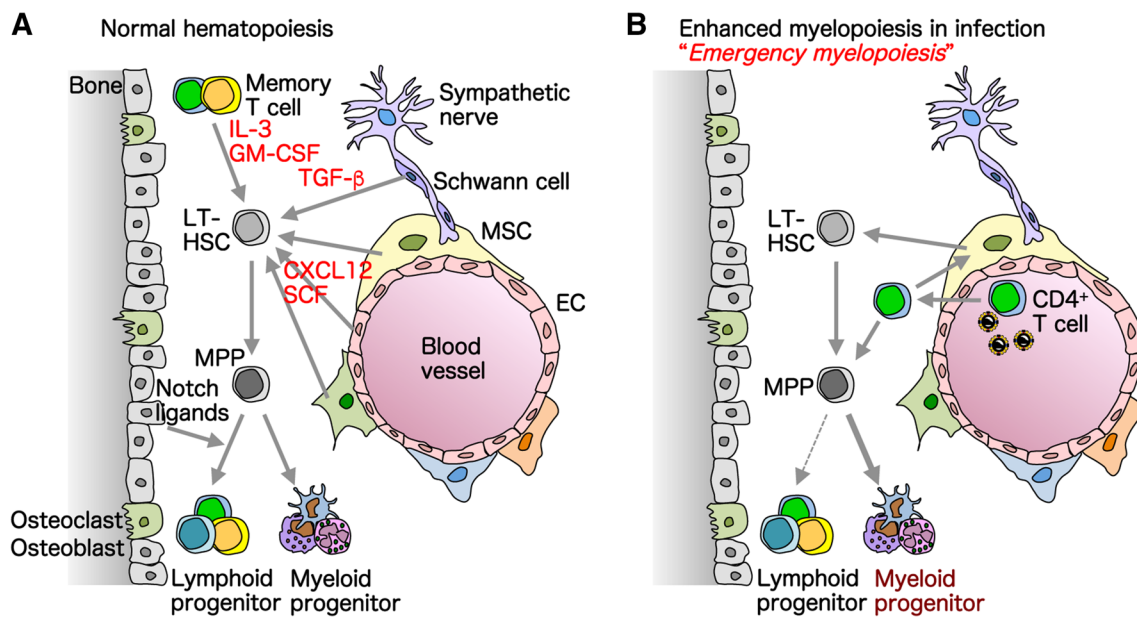
cells (MSCs), T cells, B cells, dendritic cells (DCs), and macrophages contribute to maintenance of the BM niche (Fig. 1a). Most HSCs reside in close proximity to sinusoids and blood vessels in the trabecular bone area of the BM. C-X-C motif ligand 12 (CXCL12) and stem cell factor (SCF), which are produced by ECs and perivascular cells in the BM, play critical roles in HSC maintenance [5–7]. BM-resident memory-type CD4<sup>+</sup> and CD8<sup>+</sup> T cells localized in the trabecular bone area promote the formation of the perivascular BM niche by secreting cytokines necessary for HSC maintenance, such as interleukin (IL)-3 and granulocyte macrophage colony-stimulating factor (GM-CSF) [8]. In addition, nonmyelinating Schwann cells located around the blood vessels in the BM maintain HSC dormancy by secreting transforming growth factor- $\beta$  [9].

### Emergency myelopoiesis

Although adaptive immune cells such as T cells and B cells can vigorously proliferate in an antigen-specific manner, myeloid cells such as macrophages and neutrophils need to be replenished from hematopoietic stem and progenitor cells (HSPCs) in BM because of their low proliferative activity. HSCs are predominantly quiescent, but they are activated and enter the cell cycle in response to inflammatory signals evoked by severe systemic infection or injury. Such inflammatory signals induce “emergency myelopoiesis,” which triggers differentiation of HSPCs and counterbalances the loss of cells (Fig. 1b) [10–14]. HSCs eventually give rise to lineage-restricted hematopoietic progenitors, which replenishes mature blood cells, preferentially the myeloid lineage in the process of emergency myelopoiesis. Similar to immune cells, HSPCs can be activated by TLR ligands and inflammatory cytokines [14]. Many immune and nonimmune cells, including HSPCs and ECs, express TLRs and cytokine receptors. Activation of these receptors on these cells leads to production of several proinflammatory cytokines and chemokines that promote emergency myelopoiesis.

### Purpose

Thus, homeostasis of HSCs is tightly regulated by signals such as cytokines and TLR ligands expressed by the BM niche. However, aberrant signals to HSPCs induce hematopoietic failure, often resulting in blood diseases including chronic inflammatory diseases and hematological malignancies [15–17]. Therefore, it is crucial to clarify how proinflammatory cytokines and TLR ligands regulate HSC function, expansion, and differentiation under pathogenic conditions. The detailed roles of TLRs in myelopoiesis and their underlying molecular mechanisms are beyond the scope of this review, but they have been described in other excellent reviews [18, 19]. Recently, we found that IL-27,



**Fig. 1** Regulation of myelopoiesis under homeostatic and pathogenic conditions. **a** Under normal homeostatic hematopoiesis, HSCs reside in the perivascular region of the BM, the so-called BM niche, and MSCs, ECs, and pericytes regulate HSC dormancy and differentiation through cytokines and cell contact-dependent signals such as Notch. **b** In severe infection, myeloid cells need to be replenished

from HSCs and progenitors in BM because of their low proliferative activity, a process called emergency myelopoiesis. HSCs can directly sense the presence of pathogens via pattern recognition receptors such as TLRs and proinflammatory cytokines, and they expand and differentiate into mature myeloid cells to control the infection

one of the IL-6/IL-12 family cytokines, has a unique ability to directly act on HSCs and promote their expansion and differentiation into myeloid progenitors, resulting in enhanced emergency myelopoiesis to control malaria infection [20, 21]. Here, we focus on only proinflammatory cytokines including type I and II interferons (IFNs), gp130-related cytokines such as IL-6 and IL-27, G-CSF, M-CSF, and IL-1, which have provided us new and important insights into the regulation of myelopoiesis. We summarize these recent advances in this review.

## Type I IFNs, IFN- $\alpha/\beta$

### Characteristics: anti-viral and antiproliferative cytokines

IFNs are anti-viral cytokines produced by host cells in response to viruses, bacteria, parasites, and tumors [22]. Type I IFNs, which include multiple types of IFN- $\alpha$  and a single IFN- $\beta$ , are produced broadly by various types of cells, such as fibroblasts and monocytes, and inhibit production and replication of viral RNA and DNA. The cell surface receptor complex IFN- $\alpha/\beta$  receptor is composed of IFN- $\alpha$  receptor (IFNAR)1 and IFNAR2 subunits. Type I IFNs induce an antiproliferative, proapoptotic state that prevents hosts from being infected. IFN- $\alpha$  is used to treat chronic

myeloid leukemia as well as hepatitis B and C, because type I IFNs induce direct and indirect antiproliferative effects on immature hematopoietic cells in vivo.

### Roles in infection: proliferative, and suppressive effects of IFN- $\alpha$ on HSC functions by acute and chronic stimulation, respectively

The impact of IFN- $\alpha/\beta$  on hematopoiesis was mainly investigated using a viral infection model with lymphocytic choriomeningitis virus (LCMV) and injection of poly(I:C), an inducer of type I IFN signaling, IFN- $\alpha$  itself, or mice deficient for IFN- $\alpha/\beta$  and IFNAR subunits. The effects of infection with noncytopathic LCMV on hematopoiesis in the BM using IFNAR-deficient and IFNGR-deficient mice was previously investigated [23]. The infection greatly reduced the cellularity of hematopoietic progenitors in the BM of wild-type mice and IFNGR-deficient mice but not in IFNAR-deficient mice, indicating that IFN- $\alpha/\beta$ , but not IFN- $\gamma$ , plays a critical role in the transient BM aplasia during acute LCMV infection. The role of IFN- $\alpha/\beta$  in hematopoiesis was also explored using mice deficient for IFN regulatory factor 2, a transcriptional suppressor of type I IFN signaling, IFN- $\alpha$  induced proliferation and exhaustion in HSCs, and IFN regulatory factor 2 preserved their self-renewal and multilineage differentiation capacity [11]. In addition, injection of poly(I:C) or IFN- $\alpha$  induced HSC proliferation, but chronic

type I IFN signaling further reduced the number of quiescent HSCs. Intriguingly, combined treatment with poly(I:C) and the antiproliferative chemotherapeutic agent 5-fluorouracil augmented exogenous HSC engraftment and hematopoietic reconstitution, leading to improvements in BM transplantation. Another murine study also demonstrated that HSCs efficiently exit  $G_0$  and enter an active cell cycle in response to treatment with IFN- $\alpha$  through signal transducer and activator of transcription (STAT) 1 and PKB/Akt pathways together with up-regulation of stem cell antigen-1 (Sca-1) [12]. Interestingly, dormant HSCs were shown to be resistant to 5-fluorouracil, whereas HSCs pre-treated or primed with IFN- $\alpha$  and thus induced to proliferate were efficiently eliminated by 5-fluorouracil exposure. Conversely, competitive repopulation assays revealed that HSCs chronically activated by IFN- $\alpha$  are functionally compromised and rapidly outcompeted by IFNAR-deficient cells. Thus, chronic activation of IFN- $\alpha$  signaling in HSCs impairs their function, whereas acute IFN- $\alpha$  treatment promotes the proliferation of dormant HSCs in vivo, raising the possibility of new applications for combination therapy with IFN- $\alpha$  and antitumor agents to target cancer stem cells. Cancer stem cells are considered to be the main reason for failure of treatment and relapse [24–26]. Irradiation and cytotoxic drugs cannot induce their cell death, because their mechanism of action requires active cell division, which is absent in dormant cells. In addition, HSCs express drug efflux proteins that are critically important for multidrug resistance. Consistent with these results, it was also demonstrated that HSCs transiently proliferate in response to acute IFN- $\alpha$  exposure, but chronic IFN- $\alpha$  exposure rapidly makes these HSCs return to quiescence to avoid being killed by IFN- $\alpha$  [27]. This phenomenon may serve as a safeguard mechanism to ensure survival of the HSC pool during chronic IFN- $\alpha$  exposure.

Because infections are also associated with a high risk of extensive platelet consumption, the mechanism coordinating the rapid regeneration of the platelet pool during infection using poly(I:C) was investigated [28]. In response to acute inflammation induced by poly(I:C), stem-like megakaryocyte-committed progenitors became activated and matured, producing megakaryocyte proteins from pre-existing transcripts and leading to an efficient replenishment of platelets that were lost during inflammation. Thus, an emergency machinery counteracts life-threatening platelet depletions through type I IFNs during acute inflammation.

## Type II IFN, IFN- $\gamma$

### Characteristics: antiproliferative, proapoptotic, and immune stimulatory cytokine

Type II IFN is IFN- $\gamma$ , an immune IFN that is produced by T cells and natural killer (NK) cells activated by IL-12 [29]. The receptor consists of IFNGR1 and IFNGR2. IFN- $\gamma$  plays a critical role in cellular immune responses against pathogens via up-regulation of MHC class I and II, augmentation of Th1 immune responses, and activation and differentiation of macrophages [30, 31]. In addition, IFN- $\gamma$  induces an antiproliferative, proapoptotic state that prevents hosts from being infected.

The role of IFNs, especially IFN- $\gamma$ , in HSC regulation is more complex and controversial, with several conflicting reports of positive and negative effects on hematopoiesis. Although its inhibitory effects on hematopoiesis and suppressive effects on hematopoietic progenitors were previously reported [32, 33], IFN- $\gamma$  was also demonstrated to stimulate HSC proliferation in synergy with other cytokines such as IL-3 and IL-6 [34, 35]. However, comparing these results is difficult, because the HSC markers used in each study differ. In particular, Sca-1 is an IFN-responsive molecule and highly up-regulated on many hematopoietic cells in response to IFNs [27, 36, 37]. Therefore, lineage<sup>-</sup>Sca-1<sup>-</sup>c-Kit<sup>+</sup> (LS<sup>-</sup>K) cells, which are generally myeloid-restricted progenitor cells, become positive for Sca-1 and cannot be distinguished from the real multipotent lineage<sup>-</sup>Sca-1<sup>+</sup>c-Kit<sup>+</sup> (LSK) cells, hence contaminating the LSK population and confounding analysis of it. Alternatively, these discrepancies also may be explained by compensatory mechanisms including IFN-mediated secretion of other cytokines such as IL-6 [38], IL-27 [21], and fms-related tyrosine kinase 3 ligand [39].

### Roles in infection: indirect proliferative effects of IFN- $\gamma$ on HSPCs promoting emergency myelopoiesis

The impact of IFN- $\gamma$  on hematopoiesis was mainly investigated using infection models with various pathogens and injection of IFN- $\gamma$  itself, or mice deficient for IFN- $\gamma$  and IFNGR subunits. Th1 cell products, but not those of Th2 cells, were shown to induce a rapid expansion of LSK cells in vivo and in vitro in an IFN- $\gamma$ /STAT1-dependent manner [40]. The IFN- $\gamma$ -induced LSK cells showed increased ability to bias toward myeloid cell differentiation. Moreover, a study using a mouse model of *Mycobacterium avium* infection showed that an increased proportion of not only intermediate blood progenitors, but also long-term



repopulating HSCs (LT-HSCs), proliferate during the infection via IFN- $\gamma$ -dependent, but IFN- $\alpha$ -independent, signaling [13] (Fig. 2A). IFN- $\gamma$  was sufficient to promote LT-HSC proliferation in vivo, and HSCs from IFN- $\gamma$ -deficient mice had a lower proliferative rate, indicating that IFN- $\gamma$  plays critical roles as a regulator of HSCs during both homeostasis and infection. A mouse model of the emerging tick-borne disease ehrlichiosis was used to address how infection affects hematopoietic function [41]. Infection with the intracellular bacterium *Ehrlichia muris*, which causes anemia and thrombocytopenia, was demonstrated to induce the transient proliferation and expansion of BM LSK cells via IFN- $\gamma$  signaling, accompanied by a loss of dormant LT-HSCs and a bias toward myeloid cell differentiation. Thus, inflammatory signals elicited during acute infection promote HSCs to undergo a rapid, IFN- $\gamma$ -dependent, transient shift from dormancy to proliferation and expansion, resulting in augmented emergency myelopoiesis to control the infection. A possible molecular mechanism whereby IFN- $\gamma$  impairs maintenance of HSCs by directly reducing their proliferative ability as well as the restoration of HSC numbers upon LMCV infection was examined [36]. IFN- $\gamma$  was demonstrated to reduce thrombopoietin-mediated phosphorylation of STAT5, an important positive regulator of HSC self-renewal, in a manner dependent on suppressor of cytokine signaling 1. This finding may partly explain BM failure in chronic inflammatory conditions such as aplastic anemia and HIV. However, when HSCs sense external stimuli, their adhesion status is also critical for determining HSC fate. The cell surface integrin  $\alpha\beta3$  is activated through adhesion of HSCs to extracellular matrix and niche cells, and the signaling through this integrin contributes to the maintenance of HSCs by stimulating long-term repopulating activity in collaboration with thrombopoietin [42]. Nevertheless, the suppressive effect of IFN- $\gamma$  on HSCs was recently demonstrated to be further intensified by integrin  $\alpha\beta3$  via enhanced activation of STAT1 through the augmentation of serine 727 phosphorylation [43].

Myeloid cells play a critical role in the resolution of red blood cells (RBCs) infected with malaria parasite. After infection with the mouse malaria parasite *Plasmodium (P.) chabaudi*, an IL-7 $\alpha^+$ c-Kit<sup>high</sup> progenitor subset emerges that has both lymphoid and myeloid potential in vitro [44]. After transfer into malaria-infected mice, the progenitors were demonstrated to give rise to mainly myeloid cells that are important for the clearance of infected erythrocytes via IFN- $\gamma$  signaling in hematopoietic progenitors. Moreover, the importance of the earliest myeloid-restricted progenitors in acute infection with *P. chabaudi* was noted [37]. The rapid disappearance of these infection-induced myeloid progenitors from the BM was revealed to be accompanied by contraction of the functional myeloid potential

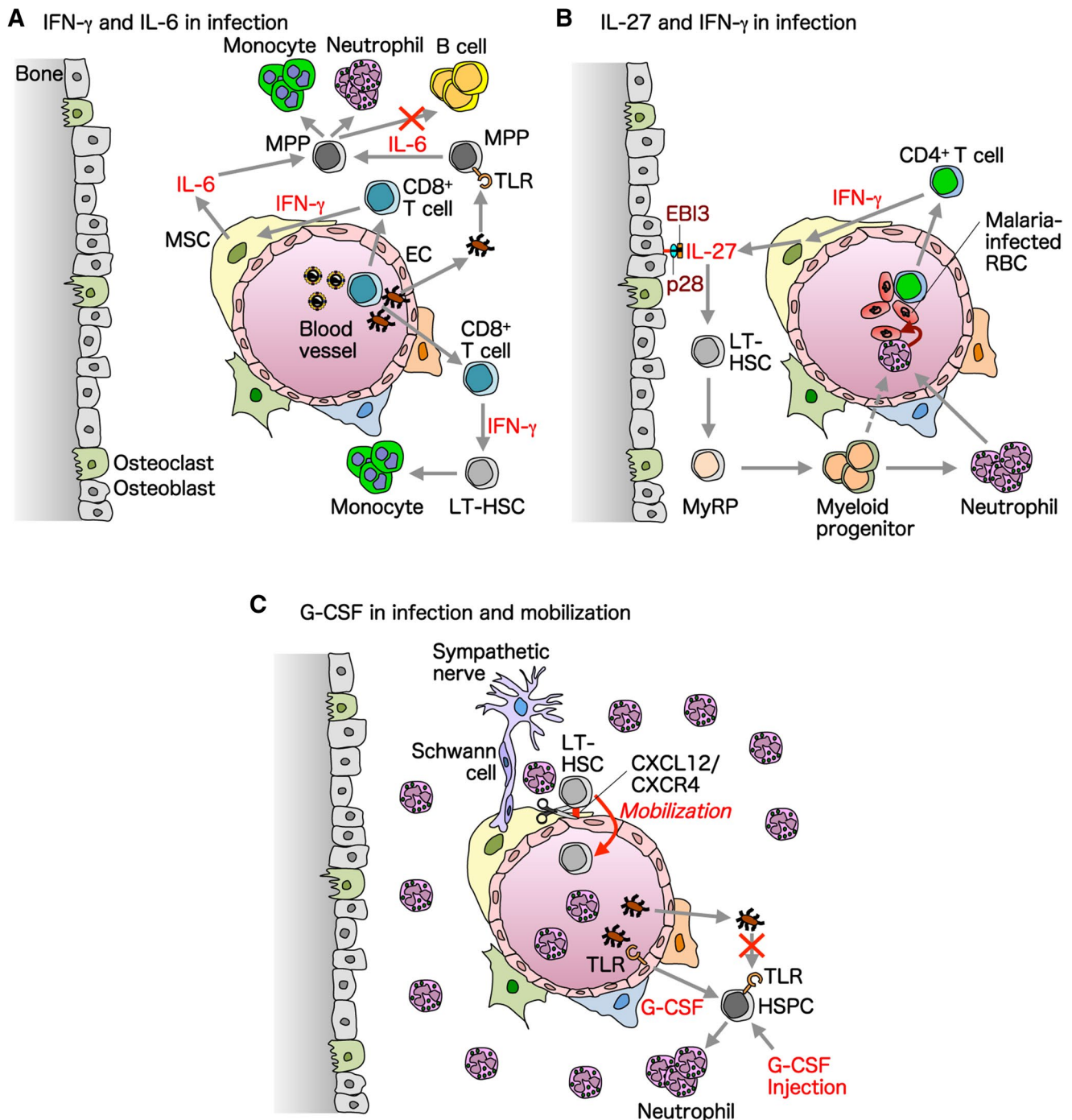
in the BM. This process was highly dependent on IFN- $\gamma$  but independent of TLR in an irradiation-resistant stromal compartment; in addition, IFN- $\gamma$  was crucial for mobilization of CCR2-expressing HPSCs out of the BM through IFN- $\gamma$ -induced chemokines, thereby transiently establishing myelopoiesis in the spleen to resolve malaria-infected RBCs.

Although IFN- $\gamma$  thus controls HSC activation, the underlying molecular mechanism remains largely unknown. The IFN-inducible GTPase *Irgm1* (*Irgm1*), a critical molecule for host defense, was revealed to inhibit baseline HSC proliferation and to be necessary for a normal HSC response to chemical and infectious stimuli [45]. *Irgm1*-deficient HSCs were over-proliferating and severely impaired in functional repopulation assays. The molecular basis for these defects was further investigated, and it was found that *Irgm1*-deficient HSCs showed up-regulation of IFN-response and cell-cycle genes [46]. The defects in hyperproliferation, self-renewal, and autophagy of *Irgm1*-deficient HSCs were normalized in *Irgm1*/IFN $\gamma$ R1- and *Irgm1*/STAT1-double-knockout mice, and the number of HSCs was reduced in aged *Irgm1*-deficient mice. Thus, negative feedback inhibition of IFN signaling by *Irgm1* is necessary to prevent hyperproliferation and depletion of HSCs, preserving HSC number and function.

## IL-6

### Characteristics: a multifunctional cytokine important for regulation of hematopoiesis as well as immune responses

IL-6 is a multifunctional cytokine that plays critical roles in the immune system as well as in a variety of biological processes including hematopoiesis. It is a primary regulator of both acute and chronic inflammation [47]. The IL-6 receptor consists of a ligand-binding IL-6-receptor  $\alpha$  chain (IL-6R $\alpha$ ) and signal-transducing subunit  $\beta$ -receptor glycoprotein 130 (gp130), where Janus kinase (JAK) 1/2, tyrosine kinase 2, and STAT3 bind. IL-6 is secreted by T cells and macrophages in response to infection, trauma, burns, and other tissue damage, resulting in inflammation. IL-6 is responsible for stimulating acute phase protein synthesis as well as the production of neutrophils in the BM. IL-6 also supports the growth of B cells, is required for resistance against various infections, and is secreted by osteoblasts to stimulate osteoclast formation. IL-6 is unique in signaling through not only membrane-bound IL-6R $\alpha$  but also sIL-6R $\alpha$  together with ubiquitously expressed gp130 [48, 49].



**Fig. 2** Roles of proinflammatory cytokines in the regulation of myelopoiesis under pathogenic conditions such as infection. **a** IFN- $\gamma$  secreted from CTLs directly acts on HSCs, thereby favoring monocytic differentiation. Moreover, IFN- $\gamma$  stimulates BM MSCs to release IL-6, which promotes monocytopoiesis from MPPs. Bacterial infection activates MPPs through TLRs to release IL-6, which promotes granulopoiesis from MPPs. **b** IL-27 is a limited unique cytokine directly acting on HSCs to promote differentiation into myeloid progenitors during emergency myelopoiesis. Among various types of hematopoietic cells in the BM, IL-27 predominantly and continuously promotes the expansion of LSK cells only, especially LT-HSCs and MyRPs with long-term repopulating activity, and differentiates them into myeloid progenitors in synergy with

SCF. Blood-stage malaria infection induces IFN- $\gamma$  production from CD4<sup>+</sup> T cells and NK cells, which may stimulate MSCs to produce IL-27. IL-27 then directly acts on HSCs and promotes the differentiation into myeloid progenitors, resulting in enhanced production of neutrophils to remove malaria-infected RBCs. **c** HSCs are held within the BM by adhesive interactions and the chemoattraction provided by CXCL12/CXCR4 signaling. G-CSF triggers the expansion of neutrophils and their precursors, creating a proteolytic environment leading to the degradation of adhesive interactions between chemokines and their receptors. Bacteria and their fragments stimulate TLR-expressing ECs but not HSPCs and consequently produce large amounts of G-CSF, which promotes enhanced proliferation of HSPCs and differentiation into neutrophils

## Roles in infection: stimulation of MPPs by IL-6 produced by MPPs and MSCs promotes emergency myelopoiesis

Although IL-6 is not necessary for maintaining homeostatic blood cell levels, it plays a critical role in hematopoietic lineage development under inflammatory conditions [50]. IL-6R $\alpha$  is expressed on MPPs and downstream myeloid progenitors, but not on LT-HSCs and short-term repopulating HSCs [51]. Stimulation of these MPPs by IL-6 dramatically induced myeloid cell differentiation while blocking the generation of CD19<sup>+</sup> B cells. The regulation of hematopoiesis by specific CD8<sup>+</sup> T cells (CTLs), which play a major role in host defense against intracellular pathogens, was further analyzed during acute LCMV infection [38]. Although IFN- $\gamma$  produced by CTLs did not primarily affect HSPCs directly, IFN- $\gamma$  promoted the production of IL-6 in BM MSCs, which increased the number of early MPPs and committed myeloid precursors in the BM, thereby promoting the accumulation of myeloid cells in the periphery and clearance of the infection (Fig. 2a). Consistent with this, HSPCs, specifically short-term repopulating HSCs and MPPs, can directly respond to bacterial components via the TLR/nuclear factor  $\kappa$ B axis and produce large amounts of cytokines including IL-6 [52] (Fig. 2a). Interestingly, the amounts produced by HSPCs were much greater than those produced by conventional immune cells such as myeloid cells and lymphocytes.

## IL-27

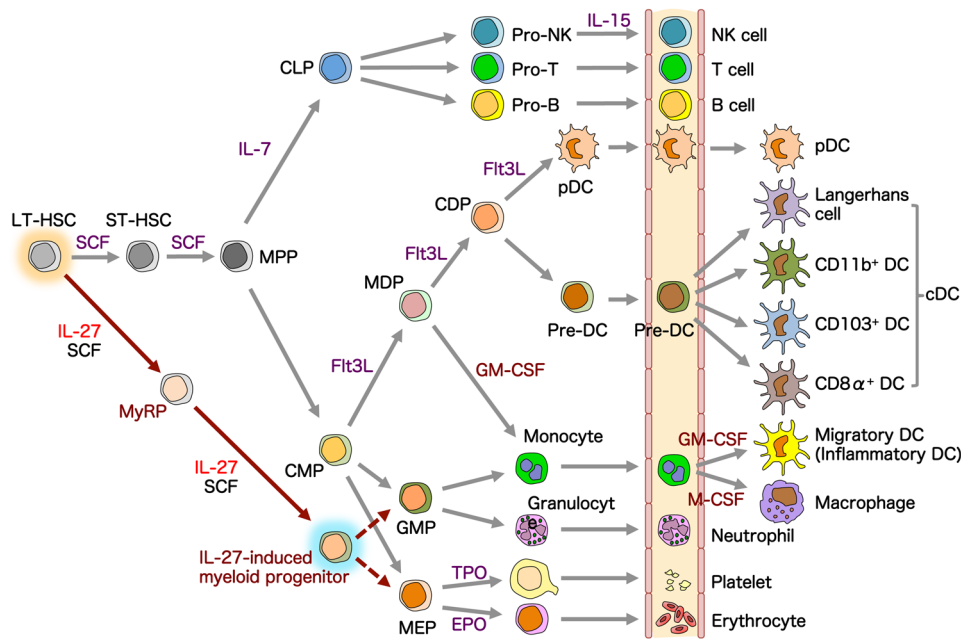
### Characteristics: a unique cytokine with both pro- and anti-inflammatory properties

IL-27 belongs to the IL-6/IL-12 family of cytokines and plays important roles in immune regulation with both pro-inflammatory and anti-inflammatory properties acting on various types of cells, such as T cells, B cells, macrophages, and DCs [53–56]. IL-27 consists of p28 and Epstein–Barr virus-induced gene 3 (EBI3), and it strongly activates both STAT1 and STAT3, which bind to respective IL-27R subunits, the unique subunit WSX-1, and gp130, a common receptor subunit in many of the IL-6 family cytokines. IL-27 augments the early induction of Th1 differentiation and CTL generation [57, 58], whereas it inhibits the differentiation of naive CD4<sup>+</sup> T cells into Th2 and Th17 cells and suppresses proinflammatory cytokine production, resulting in reduced development of allergic and autoimmune diseases. Moreover, IL-27 promotes IL-10 production by various Th cells and the generation of IL-10-producing regulatory T (Treg) cells, or Tr1 cells [59–61]. Recently, IL-27 was demonstrated to play a critical role in induction of Treg function during autoimmune inflammation [62].

## Roles in infection: a novel direct HSC-acting cytokine promoting emergency myelopoiesis

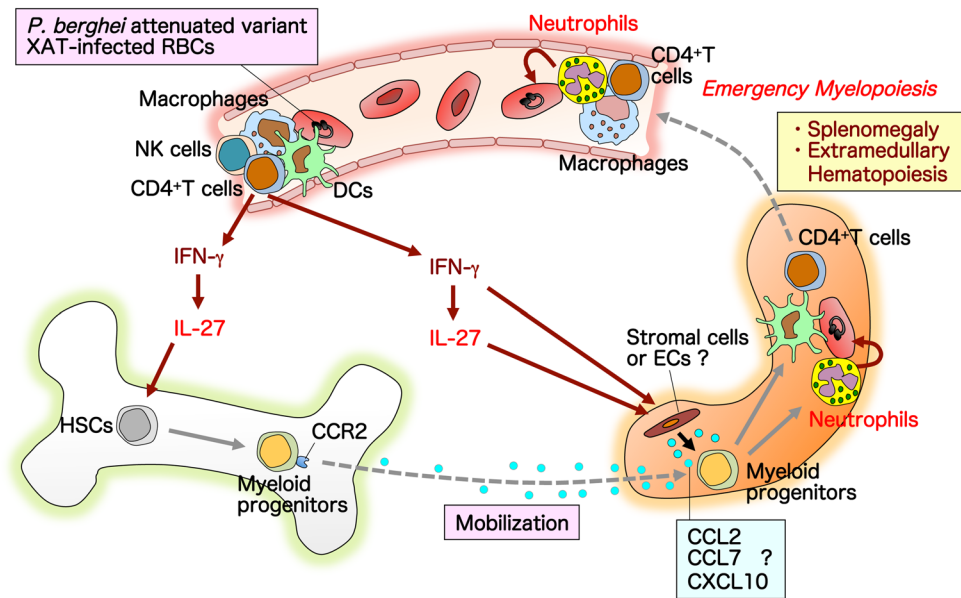
Since IL-27 can efficiently activate both STAT1 and STAT3, which are also activated by IFNs and IL-6, respectively, the role of IL-27 in hematopoiesis has logically been investigated. We first demonstrated that IL-27 in synergy with SCF directly acts on HSCs and promotes their early differentiation in vitro and in vivo [20]. A population highly enriched in mouse HSCs, CD34<sup>-</sup>KSL cells, was revealed to express both IL-27 receptor subunits, and cultures of these cells with IL-27 and SCF in vitro expanded progenitors including short-term repopulating HSCs and LT-HSCs. Transgenic mice expressing abundant IL-27 also showed enhanced myelopoiesis in the BM and extramedullary hematopoiesis in the spleen with splenomegaly [20]. Moreover, IL-27 similarly promoted the expansion and differentiation of human CD34<sup>+</sup> HSCs. Recently, we further clarified that IL-27 is a limited unique cytokine directly acting on HSCs to promote differentiation into myeloid progenitors [21] (Fig. 2b). Among various types of hematopoietic cells in BM, IL-27 predominantly and continuously promoted the expansion of LSK cells only, especially LT-HSCs and myeloid-restricted progenitor cells (MyRPs) with long-term repopulating activity, as well as differentiation into myeloid progenitors in synergy with SCF (Fig. 3). These progenitors showed enhanced potential to differentiate into migratory DCs, neutrophils, and mast cells and less so into macrophages and basophils, but not into plasmacytoid DCs, conventional DCs, T cells, and B cells. Interestingly, among various cytokines, IL-27 had the strongest ability to enhance the expansion of LSK cells and their differentiation into myeloid progenitors that retained the LSK phenotype over a long period [21].

In the blood stage of malaria infection model with the attenuated variant *P. berghei* XAT derived from the lethal strain *P. berghei* NK65, IFN- $\gamma$  production induced by IL-12 and phagocytic cells in the spleen were previously demonstrated to play critical roles in controlling parasitemia to remove infected RBCs [63, 64]. Recently, it was reported that the blood stage of *P. chabaudi* infection induces mobilization of early myeloid progenitor cells out of BM, thereby transiently establishing myelopoiesis in the spleen through IFN- $\gamma$  to resolve the infection [37, 44]. In line with these results, WSX-1-deficient mice showed more increased parasitemia than wild-type mice early in the infection with *P. berghei* XAT. The infection was revealed to enhance IL-27 expression through IFN- $\gamma$  production in the BM and spleen, and IL-27 then promoted the expansion and differentiation of LSK cells into myeloid progenitors, enhancing the production of neutrophils to control the infection [21] (Fig. 4). Thus, IL-27 is a novel cytokine that directly acts on HSCs and promotes emergency myelopoiesis.



**Fig. 3** Role of IL-27 in hematopoiesis. LT-HSCs have the capacity to self-renew over the entire life span, and they give rise to all cell types of the BM and peripheral blood. Other pluripotent progenitors (e.g., short-term repopulating HSCs and MPPs) have less self-renewal capacity. Together, these cell types mainly constitute the HSPC population. MPPs are thought to differentiate into the two main branches of hematopoietic development that are the common lymphoid pro-

genitor (CLP) and the common myeloid progenitor (CMP). IL-27 directly activates LT-HSCs and MyRPs with long-term repopulating activity together with SCF and promotes the differentiation into the myeloid progenitors, M-CSFR<sup>+</sup>Flt3<sup>-</sup>CD116/32<sup>+</sup> LSKs. CDP, common DC progenitor; GMP, granulocyte and macrophage progenitor; MDP, macrophage DC progenitor; MEP, megakaryocyte and erythrocyte progenitor



**Fig. 4** Promotion of emergency myelopoiesis during blood-stage malaria infection by IL-27. In the blood stage of malaria infection model with the attenuated variant *P. berghei* XAT derived from the lethal strain *P. berghei* NK65, IFN- $\gamma$  production induced by IL-12 and phagocytic cells in the spleen play critical roles in controlling parasitemia to remove infected RBCs. The malaria infection induces splenomegaly and extramedullary hematopoiesis by augmenting

IL-27 expression in the BM and spleen via enhanced production of IFN- $\gamma$  from T cells and NK cells. IL-27 then directly acts on HSCs and promotes their expansion and differentiation into myeloid progenitors together with SCF, resulting in increased production of neutrophils to control the malaria infection. Thus, IL-27 is a novel cytokine that directly acts on HSCs and promotes emergency myelopoiesis



On the other hand, the antitumor efficacy of IL-27 was first demonstrated by us in 2004 using a transplanted mouse tumor model [65]. Then, evidence obtained using a variety of preclinical mouse models indicated that IL-27 has potent antitumor activity against various types of tumors without apparent adverse effects through multiple mechanisms depending on the characteristics of individual tumors [66, 67]. We have recently elucidated a novel mechanism, whereby IL-27 exerts potent antitumor activity through myeloid cells [68]. Although the mouse transplantable tumor model genetically engineered to secrete IL-27 significantly decreased tumor growth [69, 70], we noticed that the number of tumor-infiltrating cells including CD11b<sup>+</sup> myeloid cells greatly increased. Similar to the results obtained in the malaria infection model [21], IL-27 was revealed to act directly on BM HSCs and promote the expansion and differentiation into myeloid progenitors, which have enhanced ability to differentiate into antitumorogenic M1 macrophages in tumor-bearing mice [68].

Supporting the effect of IL-27 on hematopoiesis in the BM, a very unique property of the p28 subunit of IL-27 was reported. This subunit has a polyglutamic acid domain, which is very similar to the acidic domain with hydroxyapatite-binding properties and bone tropism to bone sialoprotein (Fig. 2b) [71]. In addition, bone cells such as osteoclasts and osteoblasts were demonstrated to be a source of IL-27 in response to signals through TLRs and cytokines [72]. Because IL-27 has potent antitumoral activity, it could be useful for therapeutic applications targeting hematologic tumor or solid tumor metastasis with bone tropism.

## G-CSF

### Characteristics: HSC mobilizing cytokine

G-CSF was the first cytokine to be identified and rapidly enter clinical trials. G-CSF was initially used to promote the production of neutrophils in patients with chemotherapy-induced neutropenia [73, 74]. Subsequently, G-CSF was revealed to have an ability to mobilize HSCs from the BM into the blood [75, 76]. G-CSF is a cytokine that signals through its homodimer receptor, G-CSFR, and plays important roles in hematopoiesis by inducing the production of granulocytes in response to infection [77]. G-CSFR is mainly expressed in hematopoietic cells, and G-CSF activates the JAK2/STAT3 signaling pathway. The plasma G-CSF level is normally low, but rise rapidly in response to infection and subsequently decline with recovery [78, 79]. Many tissues including ECs, macrophages, epithelial cells, and fibroblasts can produce G-CSF when stimulated with inflammatory stimuli such as lipopolysaccharide, IFN- $\beta$ , and IL-17 [80, 81]. The release of G-CSF into the bloodstream

by tissues stimulates production of neutrophils within the BM and mobilization from it.

Although the response of hematopoietic cells to G-CSF is essential for HSC mobilization, the effect is indirect, and a specific response of HSCs to G-CSF is not required [82]. HSCs are held within the BM by adhesive interactions and the chemoattraction provided by CXCL12/CXCR4 signaling [83]. G-CSF triggers the expansion of neutrophils and their precursors, creating a proteolytic environment that leads to the degradation of adhesive interactions between chemokines and their receptors [84] (Fig. 2c). G-CSF also stimulates the peripheral sympathetic nervous system [85], increasing catecholamine concentrations, which in turn reduces osteoblasts as well as CXCL12 production by Nestin<sup>+</sup> MSC via effects on CD169<sup>+</sup> BM macrophages [86]. G-CSF also decreases CXCL12 production by CXCL12-abundant reticular (CAR) cells [87]. Thus, G-CSF dramatically decreases the concentrations of CXCL12 within the BM microenvironment.

### Roles in infection: HSC mobilizing cytokine essential for homeostatic granulopoiesis

G-CSF-deficient and G-CSFR-deficient mice showed a 70–90% reduction in circulating neutrophils, indicating an essential role of G-CSF in homeostatic granulopoiesis [88, 89]. In addition, because G-CSF can mediate HSPC mobilization from the BM into the circulation, it is used clinically as a mobilizing agent to prepare a source of HSC for transplantations [90]. G-CSF administration can activate dormant HSCs and increase the proportion of HSCs, resulting in the promotion of granulopoiesis [75]. Dormant HSCs are preferentially mobilized to the peripheral blood on G-CSF treatment without stimulation of their proliferation [91]. Instead, G-CSF-mediated proliferation is restricted to CD41<sup>+</sup> HSCs, which function with short term, and primarily myeloid, regenerative potential. To define which cell type is responsible for G-CSF-dependent mobilization, a series of chimeric mice were generated and analyzed using BM transplantation. Expression of the G-CSFR on HSCs was not required for their mobilization by G-CSF, and thus, G-CSFR-dependent signals act in trans to mobilize HSCs from the BM [82]. Another study used tissue-specific myeloid differentiation primary response gene 88 (MYD88)-deficient mice and in vivo lipopolysaccharide administration to model severe bacterial infection with *Escherichia coli* [92]. The findings revealed that endothelial cells, but not hematopoietic cells, hepatocytes, pericytes, or BM stromal cells, are required for emergency granulopoiesis, biasing of myeloid progenitors toward granulocyte–macrophage progenitors, resulting in accelerated production of neutrophils after lipopolysaccharide stimulation (Fig. 2c).

## M-CSF

### Characteristics: macrophage differentiating cytokine

M-CSF is a hematopoietic growth factor that plays important roles in the proliferation, differentiation, and survival of monocytes, macrophages, and BM progenitor cells by interacting with its receptor M-CSFR [93]. M-CSF is broadly expressed and detected in the blood circulation and regulates steady-state myelopoiesis. M-CSFR is predominantly expressed by the monocyte and macrophage lineages including osteoclasts and a subset of CD11b<sup>+</sup> DCs and their precursors [94]. In addition, M-CSFR expression is reported on neural precursors and trophoblasts [94]. Mice deficient for M-CSF or M-CSFR exhibit skeletal, sensory, and reproductive abnormalities caused by severe deficiencies in tissue macrophages and osteoclasts [95].

### Roles in infection: instructive differentiation of HSCs by M-CSF into myeloid cells

M-CSF is produced during infection and increases the generation of myeloid cells from lineage-committed progenitors. The ability of M-CSF to induce myeloid commitment divisions in HSCs is restricted by the monocytic transcription factor MafB [96]. MafB-deficient HSCs were shown to enhance sensitivity specifically to M-CSF and activate the myeloid master regulator PU.1, thereby skewing toward myeloid differentiation. In general, cell-fate choice of HSCs has been explained by the stochastic model [97]. However, M-CSF, but not GM-CSF or G-CSF, was demonstrated to directly induce the myeloid master regulator PU.1 at a single-cell level and instruct myeloid cell-fate change on mouse HSCs to myeloid cells, independently of selective survival or proliferation [98]. Of note, M-CSF did not compromise long-term repopulating activity of HSCs. Moreover, myeloablative treatment preceding HSC and progenitor cell transplantation is accompanied by severe myeloid cytopenia and increased susceptibility to infections in the lag period before hematopoietic recovery. Therefore, whether M-CSF might be effective in ameliorating myeloid cytopenias and in protecting from infection after hematopoietic cell transplantation was recently investigated [99]. M-CSF treatment during transplantation or after infection with clinically relevant pathogens *Pseudomonas aeruginosa* and *Aspergillus fumigatus* increased myelopoiesis and improved survival with decreased pathogen load, even for early infections and single-dose treatments. In contrast, G-CSF showed less efficient cell recovery and no protective activity against the pathogens. Thus,

M-CSF treatment during hematopoietic cell transplantation could be more efficient in myeloid cell commitment of HSCs with less side effects than clinically used G-CSF.

## IL-1

### Characteristics: a key proinflammatory cytokine

The IL-1 family comprises 11 cytokines that play a critical role in the initiation of proinflammatory responses to infections or sterile insults by up-regulating expression of integrins on leukocytes and ECs [100]. IL-1 consists of two related genes, IL-1 $\alpha$  and IL-1 $\beta$ , which have similar biological activities with distinct regulation. Their receptor complex is composed of IL-1RI and IL-1R accessory protein (IL-1RAP), together with downstream adaptor protein MYD88. IL-1RAP-deficient mice show completely abrogated cellular responses to IL-1 [101]. IL-1 receptor antagonist (IL-1RA) regulates IL-1 $\alpha$  and IL-1 $\beta$  proinflammatory activity by competing with them for binding sites of the receptor. IL-1 is a key proinflammatory signal that rapidly augments host defense in innate immunity, but also induces tissue destruction in autoimmune and inflammatory diseases [102].

### Roles in infection: reversible impairment of HSC function by chronic IL-1 stimulation

Acute IL-1 signaling leads to increased myeloid cell production both in culture and in response to infection, irradiation or myeloablative chemotherapy [103–105]. In contrast, chronic IL-1 production is associated with many of inflammatory diseases such as rheumatoid arthritis, type 2 diabetes, and obesity, which are characterized by severe hematological disorders including overproduction of tissue-damaging myeloid cells and chronic anemia [106–108]. The mechanism whereby IL-1 communicates with HSCs and the consequence for HSC activity was clarified [109]. In pre-clinical models, IL-1 promotes HSC differentiation biased into the myeloid lineage, in part through activation of PU.1 signaling [109]. While acute IL-1 exposure contributes to HSC regeneration after myeloablation and transplantation [109, 110], chronic exposure promotes uncontrolled HSC division, lost of self-renewal activity, and eventual exhaustion of the HSC pool [109]. However, this damaging effect was transient and recovered to a normal phenotype after withdrawal of IL-1.

## Conclusion

In the BM, which is an important site for hematopoiesis, memory T cells and antibody-producing plasma cells are recruited and retained long term. Diverse cells including

these T and B cells, ECs, osteoblasts, and MSCs constitute the BM niche. Extensive recent research has indicated that the myelopoiesis in the BM is tightly regulated by inflammatory signals elicited via proinflammatory cytokines produced from activated T cells as well as from innate myeloid cells in a cell contact-dependent manner during emergency myelopoiesis. Therefore, a better understanding of the roles of proinflammatory cytokines in myeloid hematopoiesis could open a novel avenue to develop therapies against diseases including infectious diseases and hematological malignancies.

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