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Hematopoietic progenitor cells as integrative hubs for adaptation to and fine-tuning of inflammation

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Abstract

Recent advances have highlighted the ability of hematopoietic stem and progenitor cells in the bone marrow to sense peripheral inflammation or infection and adapt through increased proliferation and skewing toward the myeloid lineage. Such adaptations can meet the increased demand for innate immune cells and can be beneficial in response to infection or myeloablation. However, the inflammation-induced adaptation of hematopoietic and myeloid progenitor cells towards enhanced myelopoiesis might also perpetuate inflammation in chronic inflammatory or cardio-metabolic diseases by generating a feed-forward loop between inflammation-adapted hematopoietic progenitor cells and the inflammatory disorder. Sustained adaptive responses of progenitor cells in the bone marrow can also contribute to trained immunity, a non-specific memory of earlier encounters that in turn facilitates their heightened response, as well as that of their progeny, to future challenges. Here, we discuss the mechanisms that govern the adaptation of hematopoietic progenitor cells to inflammation and its sequelae in the pathogenesis of human disease.

Hematopoietic stem cells (HSCs) and hematopoietic progenitor cells in the bone marrow (BM) are responsible for the maintenance of steady-state and stress-adapted hematopoiesis[1–3]. HSCs (also named long-term HSC (LT-HSCs)) reside at the top of the hematopoietic hierarchy, have self-renewal and multi-lineage differentiation capacity and give rise to all mature blood cells. LT-HSCs can differentiate into short-term HSCs (ST-HSCs) and multi-potent progenitors (MPPs), which are cells with relatively restricted differentiation potential; LT-HSCs, ST-HSCs and MPPs are collectively known as

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hematopoietic stem and progenitor cells (HSPCs)[1,4]. HSPCs are enriched within the lineage $^{-}$Sca-1^{+}c-Kit^{+} (LSK) population, wherein LT-HSCs and MPPs can be differentiated with distinct markers, for instance SLAM family markers[1,4]. MPPs differentiate to oligo-potent and uni-potent progenitor cells, such as common myeloid progenitors (CMPs), granulocyte-monocyte progenitors (GMPs) and others, which give rise to mature blood cells[2,3].

HSC maintenance is facilitated by the highly specialized niche micro-environment, comprising different cell types, such as mesenchymal stromal cells (MSC), endothelial cells (EC) and megakaryocytes[5]. The HSC niche fosters a variety of juxtracrine (cell-cell or cell-matrix) and paracrine (via cytokines, chemokines or growth factors) interactions involving the HSCs, thereby regulating the self-renewal of HSCs and instructing the differentiation of hematopoietic progenitor cells[5,6]. As an adaptation to the hypoxic niche micro-environment, HSCs preferentially engage aerobic glycolysis for energy production rather than oxidative phosphorylation; consistently, the glycolytic metabolism of HSCs promotes the maintenance of their stemness[7].

The traditional tree-like hierarchical model of hematopoiesis[1], in which lineage decision takes place at the MPP stage, is constantly redrawn. The use of new technologies, such as single-cell analysis[8–12], has resulted in alternative models of hematopoiesis that suggest a greater functional heterogeneity of HSCs (reviewed in ref.[3]). Additionally, several surface markers have been identified to characterize lineage-biased HSCs and MPPs[13,14]. For instance, based on the expression of Flt3 and CD150, MPPs may form three distinct subpopulations, which are primed towards erythro-megakaryocytic (Flt3^{-}CD150^{+}MPPs or MPP2), myeloid (Flt3^{-}CD150^{-}MPPs or MPP3) or lymphoid (Flt3^{+}CD150^{-}MPPs or MPP4) lineage[14]. Another example is the identification of CD41 as a marker of myeloid-biased HSCs[13]. Moreover, HSC clones primed for generation of megakaryocytes and platelets have been also reported[8,9].

In both humans and mice, early lineage priming of HSCs is controlled by distinct gene expression modules, which are regulated by lineage-specific transcription factors [11,15]. For example, the C/EBP family of transcription factors and PU.1 regulate the entry into myeloid lineage[15–17]. As outlined below in more detail, activation of such lineage-specific transcription factors is also critical for the adaptation of hematopoietic progenitors to inflammatory stimuli[18]. Further differentiation decisions in myelopoiesis, a process leading to the generation of specific myeloid cell subsets, granulocytes, monocytes and dendritic cells[19,20], occur at the level of myeloid progenitors[21] and are fine-tuned by additional transcription factors and epigenetic mechanisms[22–24].

Although it is debated whether HSCs contribute to unperturbed hematopoiesis[25,26], HSCs are critical for hematopoiesis reconstitution upon myeloablation. In this setting, activation of HSCs results in massively increased myelopoiesis as compared to lymphopoiesis[25]. Upon transplantation-associated hematopoietic stress, HSCs can bypass several steps of the traditional tree-like hematopoietic hierarchy via direct differentiation into myeloid progenitors through asymmetric division[12], a process giving rise to progeny cells with distinct fates, *e.g.*, a stem cell and a lineage-committed cell. Hence, upon demand (*e.g.*, following myeloablation or inflammation), HSCs rapidly respond to replenish myeloid cells

through a process designated as emergency myelopoiesis[20]. Furthermore, the rapid adaptation of hematopoietic progenitors to severe bacterial infections leading to peripheral blood neutrophilia is designated as emergency granulopoiesis[2]. Although meeting the increased demand for immune cell generation, such adaptations of hematopoietic progenitors may contribute to chronicity of inflammatory diseases[27]. Herein, we review emerging evidence that the adaptation of hematopoietic progenitor cells to inflammation acts as a central hub of the host response to infectious and inflammatory challenges.

Adaptation of hematopoietic progenitor cells to inflammation

Similar to the mature immune cells and committed myeloid progenitor cells in the BM, HSPCs can also become directly responsive to acute infection or chronic inflammatory conditions[1,2,27]. This HSPC adaptation is tightly orchestrated by a combination of cell-intrinsic (transcriptional, epigenetic and metabolic) and cell-extrinsic (soluble growth factors, cytokines, microbial ligands and adhesive interactions) mechanisms[2,28]. HSPCs are more sensitive to exogenous stimuli than traditionally thought, owing to their expression of receptors for microbial products, such as the Toll-like receptors (TLRs) and receptors for inflammatory cytokines and growth factors, such as IL-1β, IL-6, M-CSF, type 1 and 2 interferons (IFN), the abundance of which massively increases upon systemic infection, thereby enabling HSPCs to sense a systemic infectious or inflammatory challenge directly or indirectly[1,2]. While such HSPC responses can be beneficial in promoting elimination of an infection, they may also cause impairment of HSPC function and exhaustion if HSPC activation is chronically sustained[2] or may contribute to chronicity of inflammatory pathologies[27]. The underlying mechanisms and functional outcomes of HSPC adaptation to inflammatory stimuli have only now begun to be understood. Below we discuss the complex regulatory interactions at the interface between inflammation and HSCs.

Effects of TLR signaling on HSC fate decision and regulation of myelopoiesis

The seminal observation that hematopoietic progenitors express TLRs and that TLR ligation induces myeloid differentiation in a manner dependent on the adaptor MyD88 provided new insight in the role of HSPCs in the host defense against pathogens[29]. Subsequent studies have identified indirect, cytokine-mediated, and direct effects of TLR ligands on HSPCs (Fig.1). Upon activation of the TLRs, ST-HSCs and MPPs produce substantial amounts of cytokines in an manner dependent on the transcription factor NF-κB[30]. These cytokines, particularly IL-6, can promote, in a paracrine fashion, the proliferation and myeloid differentiation of HSPCs[30]. Additionally, systemic LPS administration stimulates enhanced HSC proliferation[31], while chronic low-dose LPS treatment results in expansion of HSCs and their myeloid skewing in a cell-intrinsic, TLR4-dependent manner, as shown in BM chimera experiments using cells from TLR4-deficient and -proficient mice[32]. However, chronic low-dose murine endotoxemia induces the functional impairment of HSCs and loss of quiescence, as shown by their reduced repopulation capacity in serial transplantation experiments[33]. Moreover, high-dose LPS results in increased BM cell death and dysfunction of HSCs, despite their initial expansion[34].

Hence, TLR4 activation on HSCs stimulates their proliferation, but may exert several detrimental actions on their function due to proliferative stress in HSCs upon TLR4 ligation[33,35]. Specifically, TLR4 activation stimulates the proliferation of dormant HSCs, while diminishing their self-renewal and repopulation capacity[36]. These effects are mediated by signaling dependent on the adaptor TRIF and subsequent downstream production of reactive oxygen species (ROS) and activation of the mitogen-activated protein kinase p38, leading to replication stress and activation of the DNA repair machinery[36]. Scavenging ROS or blockade of p38 prevents this endotoxemia-related HSC exhaustion[36]. Consistently, TRIF mediates the expansion and functional exhaustion of HSPCs in sepsis[35].

Different TLR ligands may lead to different emergency myelopoiesis responses by engaging distinct pathways leading to the generation of Ly6C^{hi} monocytes[37]. Specifically, stimulation of TLR4 by LPS causes an increase in neutrophils and neutrophil-like monocytes derived from GMPs, while stimulation of TLR9 by CpG results in expansion of dendritic cells and of a functionally distinct monocyte subtype derived from monocyte-dendritic cell progenitors[37]. Besides the direct effects of TLR agonists on hematopoietic progenitors, endotoxemia also induces the production of myeloid-lineage growth factors (discussed in detail below), thereby supporting the replenishment of blood neutrophils[38]. Importantly, the TLR4-MyD88 signaling pathway also mediates LPS-related emergency granulopoiesis through a paracrine pathway, which does not involve direct effects on HSPCs, but requires the production of the growth factor G-CSF by endothelial cells[38] (Fig.1), as discussed below.

Effect of growth factors on the regulation of myelopoiesis

G-CSF is a major driver of granulopoiesis under both steady-state and emergency conditions, such as infection, by regulating the expression of myeloid lineage-specific transcription factors and of receptors for myeloid lineage-specific growth factors[2,39]. Other growth factors contributing to emergency myelopoiesis are M-CSF and GM-CSF[2]. However, mice deficient in these factors (G-MCF, GM-CSF and M-CSF) can still generate modest numbers of myeloid cells, at least in response to sterile peritoneal inflammation, highlighting a functional redundancy in myelopoiesis[40]. GM-CSF may act alone or together with other cytokines, such as IL-3, in the regulation of myelopoiesis, specifically during chronic inflammation or bacterial infection[2,41].

During emergency granulopoiesis, G-CSF induces proliferative and lineage-specification signals by acting primarily on CMPs and GMPs, which expand and form well-defined clusters that differentiate into granulocytes[39,42,43]. Besides affecting the differentiation of myeloid progenitor cells, G-CSF may also induce the proliferation of HSCs[44]. Moreover, G-CSF stimulates the mobilization of HSCs from the BM in an indirect fashion, by acting on monocytes in the HSC niche[45,46]. G-CSF-induced activation of its receptor, G-CSFR, leads to signaling through the transcription factor STAT3, which directly stimulates the expression of the master transcriptional regulator of emergency granulopoiesis, C/EBPβ[39,42]; contrastingly, C/EBPα is the major driver of steady-state granulopoiesis[2]. The effects of STAT3 are counteracted by the regulator of cytokine signal transduction SOCS3, which downregulates G-CSF-induced emergency granulopoiesis; indeed, hematopoietic cell-specific deficiency of SOCS3 results in sustained G-CSF-induced activation of STAT3,

enhanced neutrophilia and mobilization of hematopoietic progenitor cells[47]. Consistently, the epigenetic modifier TET2, which is mutated in patients with myeloid malignancies[48], promotes infection-induced emergency myelopoiesis by suppressing the expression of SOCS3[49].

The generation of monocytes in the BM occurs in a manner dependent on the receptor CSFR1, which binds M-CSF[50]. M-CSF acts directly on hematopoietic and myeloid progenitor cells and induces their differentiation into monocytes (Fig.1). *In vitro* treatment of GMPs with M-CSF promotes their differentiation to mature monocytes[51]. The M-CSF-instructed monocyte lineage choice in GMPs is mediated by Src family kinase signaling[52]. M-CSF can instruct myeloid lineage identity in single HSCs, independently of HSC survival or proliferation, by inducing a PU.1-dependent molecular signature[53]. This mechanism of M-CSF-dependent myelopoiesis may protect against opportunistic infections post-HSC transplantation[54].

Effect of IFN on HSCs fate decision and the regulation of myelopoiesis

Type 1 IFN, especially IFN-α, and type 2 IFN (IFN-γ) are central cytokines in the adaptation of HSPCs to inflammation. The type 1 IFN inducer polyinosinic:polycytidylic acid (polyI:C), or IFN-α itself, can drive proliferation of dormant HSCs (Fig.1) through a pathway dependent on the IFN-α/β receptor IFNAR and STAT1; however, chronic administration of IFN-α results in impaired HSC repopulation capacity[55]. The transcription factor Irf2, a negative regulator of type 1 IFN signaling, counteracts the effects of type 1 IFN on HSCs and protects quiescent HSCs from type 1 IFN-induced proliferation-associated exhaustion[56]. This type 1 IFN-dependent functional impairment and attrition of HSCs is due to induction of DNA damage in HSCs entering the cell cycle, which is associated with enhanced mitochondrial membrane potential and mitochondrial production of ROS[57]. However, type 1 IFN-triggered proliferation of HSCs may be brief, due to the transient reduction in the expression of genes enforcing quiescence (*e.g., p27, p57, Foxo1, Foxo3a* or *Pten*), while reestablishment of HSC quiescence can protect them from the pro-apoptotic effects of IFN-α[58]. Hematopoietic cells may engage additional homeostatic protective mechanisms against IFN-α-induced dysfunction. For example, all-trans retinoic acid-induced signaling protects dormant HSCs against polyI:C-induced replicative stress[59]. The cyclic GMP-AMP (cGAMP) synthase cGAS is an intracellular sensor of pathogen-derived DNAs, mostly from viruses. Upon DNA binding, cGAS generates cGAMP, which – together with the adapter STING – stimulates the production of type 1 IFN[60]. Interestingly, a circular RNA antagonizing cGAS synthase activity, named cia-cGAS, is highly enriched in the nucleus of LT-HSCs and promotes maintenance of their dormancy by protecting HSCs against cGAS-type 1 IFN-mediated exhaustion[61]. The complexity of the IFN-α effects on the BM is further exemplified by the observations that acute IFN-α-mediated inflammation acts on HSC-niche endothelial cells, affecting vascularity and vessel leakage in the BM[62], whereas type 1 IFN can additionally stimulate proliferation and post-trancriptional protein synthesis in a primed subpopulation of stem cell-like megakaryocyte-committed progenitor cells phenotypically residing within the HSCs, leading to rapid platelet replenishment in acute inflammation[63].

IFN-γ also modulates the maintenance and proliferation of HSCs. Infection with *Mycobacterium avium* triggers the proliferation of HSCs in an IFN-γ, rather than IFN-α-dependent manner[64] (Fig.1). Consistently, HSC proliferation is abrogated in mice with genetic deficiency of either the receptor for IFN-γ or its downstream signal transducer STAT1[64], whereas administration of recombinant IFN-γ reverses the effect, suggesting that IFN-γ stimulates HSC cell cycle entry[64]. However, the effects of IFN-γ on HSCs are context-dependent, as IFN-γ inhibits the proliferation of HSCs, impairs their maintenance and negatively affects their recovery during infection with the lymphocytic choriomeningitis virus (LCMV)[65]. In the context of LCMV infection, IFN-γ induces myeloid differentiation by acting either directly on myeloid-biased HSC[66] or indirectly; specifically, IFN-γ from cytotoxic T cells stimulates a paracrine pathway leading to enhanced production of IL-6 from BM-MSCs, resulting in heightened proliferation and myelopoiesis of MPPs[67]. Additionally, IFN-γ is responsible for the attrition of HSCs due to their differentiation into myeloid cells and loss of their self-renewal capacity during chronic mycobacterial infection in mice[66]. Furthermore, intravenously administered mycobacterial Bacille Calmette-Guérin (BCG) triggers the IFN-γ-dependent expansion of HSPCs and their myeloid differentiation through a myelopoiesis-related transcriptional program[68] (Fig.1).

IL-1β and other cytokines effects on HSCs fate decision

IL-1β, a central mediator in innate immunity[69], acts directly on HSCs *in vitro*, promoting their proliferation and myeloid differentiation through activation of the transcription factor PU.1[18] (Fig.1). Administration of IL-1β to mice results in increased numbers of myeloid-biased HSPCs, while BM recovery after chemotherapeutic injury is delayed in IL-1 receptor-deficient mice[18]. Chronic administration of IL-1β diminishes the self-renewal capacity of HSCs, although this effect is reversed upon IL-1β withdrawal[18]. IL-1β, in fact, may account for the hematologic abnormalities in patients with X-linked chronic granulomatous disease (X-CGD) and in the respective mouse model, both of which are characterized by IL-1β-associated hyperinflammation[70]. Patients with X-CGD have decreased HSC counts, whereas mice with targeted disruption in the X-linked gene gp91^{phox} have increased HSC proliferation and impaired reconstitution capacity, as well as boosted myelopoiesis, as assessed by enhanced numbers of GMPs[70]. An IL-1 receptor antagonist partially restores hematopoiesis in mice with X-CGD[70], suggesting IL-1 signaling is in part responsible for this phenotype. Short-term or low-dose administration of IL-1α or IL-1β prevents chemotherapy-induced myelosuppression[71,72] and protects cyclophosphamide-induced neutropenic mice against sepsis[72], indicating timing and dosing may be critical regulators of the beneficial or detrimental effects of IL-1 on HSCs. While IL-1 may promote restoration of myelopoiesis, persistent IL-1-mediated inflammation negatively impacts HSC functionality.

Tumor necrosis factor (TNF) induces proliferation and instructs myeloid lineage decisions in HSCs and may thus compromise their repopulation capacity[73]. TNF directly upregulates PU.1 *in vitro* and mediates its activation in LPS-administered mice, because PU.1 is not affected by LPS in TNF-deficient mice[74]. IL-3, derived from innate response activator B cells, amplifies myelopoiesis and inflammation in sepsis. Specifically, the expansion of HSPC and myeloid progenitor cells is hindered by IL-3 deficiency in murine sepsis, while high

concentrations of IL-3 in plasma correlate with higher mortality in human sepsis[75]. IL-6 regulates HSPC proliferation and differentiation during emergency myelopoiesis[2,30]. In this context, IL-6 may be derived either from the HSPCs following TLR stimulation[30] (Fig.1) or from BM-MSCs upon stimulation with cytotoxic T cell-derived IFN-γ[67]. IL-6, through activation of signaling though SHP2 and STAT3, can also support survival of TET2-deficient HSPCs and myeloid cells[76]; as TET2 mutations are linked with clonal hematopoiesis and a higher risk for leukemia development, these observations may indicate how inflammation may promote survival of preleukemic HSPCs[76]. IL-27, a member of the IL-6-IL-12 cytokine family, also acts on HSPCs and promotes emergency myelopoiesis[77]. In a model of malarial infection, deletion of the IL-27R subunit WSX-1 suppressed the expansion of progenitor cells and their differentiation into myeloid cells, which resulted in increased parasitemia[77].

Modulation of inflammation-induced HSPC adaptation by the BM niche

Emergency myelopoiesis is also regulated by the HSC niche microenvironment in the BM. The niche modulates HSC quiescence, self-renewal, proliferation and differentiation into committed progenitor cells[5,28,78,79] (Fig.2). Niche cells such as endothelial cells, nestin$^+$ MSCs, perivascular stromal cells, including CXCL12-abundant reticular (CAR) cells, and osteolineage cells regulate HSC function through paracrine signals (growth factors or chemokines) or through adhesive interactions that may also involve extracellular matrix proteins[5,28,78,79]. DEL-1, an adhesive protein secreted by niche endothelial cells, CAR cells and osteolineage cells in the BM interacts with β3 integrin on HSCs and enhances the proliferation of LT-HSCs and their myeloid differentiation, predominantly in the context of LPS- or G-CSF-induced stress myelopoiesis[80]. Another matrix-associated protein, osteopontin, restrains emergency myelopoiesis in favor of lymphopoiesis through a dual mechanism mediated by two distinct isoforms: intracellular osteopontin is pro-apoptotic in myeloid progenitors, whereas secreted osteopontin is anti-apoptotic in differentiated lymphoid cells[81]. Furthermore, BM innervation and sympathoadrenergic activity are important HSC niche regulators and control the circadian HSC release into the circulation; conversely, loss of sympathoadrenergic nerves promotes aging of the niche and impairs regeneration of hematopoiesis[82–84].

The progeny of HSCs in the BM may be important mediators for the adaptation of HSPC to inflammatory signals. Monocytes are a major cellular target of G-CSF-induced egress of HSPCs from the BM niche and emergency granulopoiesis[46]. G-CSF-induced mobilization of HSPCs is linked with depletion of trophic endosteal macrophages in the BM[85]. CD169$^+$ macrophages in the BM may interact with osteoblasts or nestin$^+$ cells in the niche to control expression of trophic factors such as angiopoietin-1, CXCL12 and Kit ligand on HSC and retention of HSPC in the niche[85,86]. Consistently, depletion of BM macrophages is sufficient to induce HSPC mobilization[85]. α-SMA$^+$ monocytes and macrophages may protect HSPCs from exhaustion in stress conditions such as sublethal irradiation, in part because PGE2 produced from these macrophages upregulates nestin$^+$ stromal cell-derived CXCL12, which is critical for stem-cell quiescence[87]. BM macrophages can also regulate the HSC niche through the phagocytosis of apoptotic cells (known as efferocytosis). Senescent neutrophils in the circulation upregulate their expression of CXCR4 and home back to the BM, where

they are efferocytosed by BM-resident $CD169^+$ macrophages, a process that in turn promotes the circadian egress of hematopoietic progenitor cells into the circulation[88] (Fig.2).

Neutrophils and their precursors in the BM also contribute to demand-adapted myelopoiesis. In response to systemic inflammation, $Gr1^+$ myeloid cells in the BM release ROS, which stimulates the proliferation and differentiation of myeloid progenitor cells, thus enhancing myeloid cell output[89]. Granulocyte-derived TNF promotes vessel growth and thereby HSPC regeneration[90]. Megakaryocytes regulate HSC quiescence through TGFβ1 or CXCL4 and may promote post-injury regeneration of HSCs through FGF-1[91,92]. Megakaryocytes preferentially regulate the proliferation of vWF^+ platelet- and myeloid-biased HSCs[93]. In vivo high-resolution imaging revealed the co-localization of HSPCs with $CD4^+CD25^+FoxP3^+$ regulatory T cells (T_{reg} cells) that accumulate on the endosteal BM niche[94]. These T_{reg} cells may confer immune privilege to the HSPC niche, thus preventing allogeneic rejection of transplanted HSPCs or protecting endogenous HSPCs from excessive inflammation. In support of this notion, a niche-specific subpopulation of $CD150^{hi}$ T_{reg} cells promotes HSC quiescence and engraftment of HSCs through a mechanism dependent on adenosine generated by the ectoenzyme CD39, which protects HSCs from oxidative stress[95] (Fig.2). Together, different cells in the HSC niche contribute to context-dependent HSPC adaptation to diverse inflammatory challenges.

The effect of trained immunity on HSPCs

Trained immunity is a form of adaptation that enhances the response of innate immune cells to secondary challenges independently of adaptive immunity[96,97]. Trained immunity can be triggered by certain microbial components, such as the fungal cell-wall constituent β-glucan or vaccines like BCG, and involves immunometabolic and epigenetic alterations in target cells[96,97]. Trained innate immunity operates in hematopoietic progenitor cells[68,98], resolving an earlier paradox regarding the long-term effect of trained immunity in myeloid cells with a relatively short lifespan. Trained immunity induced by injection of β-glucan in mice leads to the expansion of myeloid-biased HSPCs, such as $CD41^+$LT-HSCs and MPP3 cells, in the BM[98]. β-glucan-induced myelopoiesis requires signaling through IL-1β and is associated with enhanced glycolysis and cholesterol biosynthesis in HSPCs. Increased cholesterol amounts in HSPCs from β-glucan-trained mice results in enhanced signaling via CD131, the common β-subunit of the IL-3/GM-CSF receptor (IL-3Rβ), in LT-HSCs and MPPs[98]. Consistently, elevated expression of IL-3Rβ and enhanced myeloid bias are observed in HSPCs upon blockade of cholesterol efflux[99]. Importantly, β-glucan-induced training of HSPCs and enhancement of myelopoiesis confers a favorable outcome to secondary systemic LPS challenge and protection against chemotherapy-induced myelosuppression[98] (Fig.1). BCG administration in mice also stimulates the expansion of HSPCs and promotes myelopoiesis in a manner requiring IFN-γ signaling. Importantly, macrophages derived from BCG-trained progenitor cells mediate host protection against *Mycobacterium tuberculosis* infection independently of adaptive immunity[68] (Fig.1). Hence, innate immune training of hematopoietic progenitor cells[68,98] shares common features with emergency myelopoiesis in response to systemic infection or inflammation[2].

HSC expansion due to inflammatory stimuli such as LPS or IFN-α leads to exhaustion of HSCs, which is associated with compromised self-renewal and capacity for competitive repopulation and is mediated by DNA damage associated with replication stress[35,36,57,100]. Interestingly, β-glucan-triggered training of HSPCs is associated with attenuated LPS- or chemotherapy-induced replication stress in HSCs[98]. The beneficial effect of trained immunity in this case may lie in changes in cellular metabolism. While mitochrondrial ROS and activation of oxidative phosphorylation are associated with DNA damage in HSCs and lead to their functional impairment, LT-HSC maintenance depends on glycolysis[7,57,101,102]. HSPCs in β-glucan-trained mice retain a glycolytic signature even after chemotherapy, which may be linked with resistance to replication stress-related DNA damage[98]. This could suggest that certain agonists of trained immunity may act favorably on HSCs and myelopoiesis by counteracting inflammation-dependent stress and impaired function in HSC[98]. Genetic targeting of the pathways implicated in trained immunity, such as IL-1 signalling or cell metabolism in hematopoietic progenitor cells, mature myeloid cells and components of the HSC niche are required to clarify the mechanisms underlying the modulation of myelopoiesis by trained immunity.

Adaptation of hematopoietic progenitors in inflammatory diseases

There is increasing evidence that chronic metabolic-inflammatory conditions, such as obesity and diabetes, or cardiovascular-inflammatory conditions, such as atherosclerosis can alter hematopoiesis. Reciprocally, adaptation of hematopoietic progenitor cells leading to chronic leukocytosis may contribute to the perpetuation and chronicity of these disorders[27,103,104] (Fig.3). Diabetes-associated hyperglycemia and obesity result in monocytosis and neutrophilia in mice[105,106]. In hyperglycemia, the neutrophil-derived damage-associated molecular pattern S100A8/A9 interacts with the receptor RAGE on CMPs and triggers the production of M-CSF and GM-CSF, which stimulate the proliferation of GMPs and in turn, monocytosis, neutrophilia and atherosclerosis[105]. Similarly, genetic or diet-induced obesity in mice stimulates the proliferation of myeloid progenitor cells in the BM, in a manner dependent on the NLRP3-inflammasome-dependent production of IL-1β in adipose tissue (AT) macrophages[106] (Fig.3). Weight loss in humans following bariatric surgery significantly decreases the number of circulating monocytes and neutrophils[106]. The myeloid bias of HSPCs from mice with diet-induced obesity is maintained upon serial transplantation to recipient mice, and the obesity-related myeloid reprogramming is associated with increased numbers of LT-HSCs and MPPs in the BM[107,108]. The myeloid-biased reprogramming of HSPCs requires signaling through TLR4, MyD88 and TRIF and contributes to enhanced generation of proinflammatory macrophages in the AT, thereby exacerbating obesity-related AT inflammation and dysfunction[107,108]. Experiments with germ-free mice have also indicated an important role of the gut microbiota in myelopoiesis[109]. In this context, altered gut microbiota in mice due to high-fat diet promotes HSPC differentiation toward myelopoiesis at the expense of lymphopoiesis through modulation of niche MSCs[110].

Altered hematopoiesis is also integral to atherosclerosis and cardiovascular disease[27,103]. Myocardial infarction (MI) results in enhanced myelopoiesis, which may involve several complementary and likely synergistic mechanisms[27] (Fig.3). For instance, a myeloid-biased

subset of HSPCs ($CCR2^{+}CD150^{+}CD48^{-}$LSKs) with a higher proliferative and lower self-renewal capacity than HSCs contributes to the enhanced myelopoiesis post-MI[111]. Increased sympathoadrenergic activity causes enhanced mobilization of HSPCs from the BM to the spleen, which becomes a site for increased extramedullary myelopoiesis[112]. Interestingly, enhanced sympathoadrenergic activity mediates the increased, stress-induced, proliferation of LT-HSCs and myelopoiesis, thus likely explaining how psychosocial stress promotes atherosclerosis[113]. In a similar context, a disturbed sleep pattern contributes to atherosclerosis by dysregulating a neuro-immune axis linking hypothalamic hypocretin to regulation of myelopoiesis[114]. IL-1β is a central player in enhanced myelopoiesis post-MI, as it can promote HSPC proliferation in a direct or indirect, niche cell-dependent fashion, as well as stimulate splenic monocytopoiesis[115,116]. Detrimental effects of innate immune training may also contribute to western diet-associated atherosclerosis[117]. Western diet induces NLRP3- and IL-1-dependent transcriptomic and epigenetic reprogramming in GMPs in atherosclerosis-prone LDL-receptor (Ldlr)-deficient mice, driving the GMPs towards enhanced proliferation and inflammatory responses; consistent with the long-term effects of trained immunity, this progenitor cell reprogramming is sustained even after mice are switched back to chow diet[117]. Moreover, GM-CSF from the infarcted myocardium stimulates expansion of myeloid-biased $CD131^{+}$ MPP3 in the BM[118].

Cholesterol biosynthesis and/or mevalonate, the first metabolite of the cholesterol biosynthetic pathway, are important mediators of innate immune training in mature myeloid cells or hematopoietic progenitor cells[98,119,120]. The cholesterol-dependent immunometabolic crosstalk during trained immunity may also be intimately linked with the dyslipidemia- or hypercholesterolemia-associated altered hematopoiesis that leads to enhanced myelopoiesis during atherosclerosis[97,103]. Disrupted cholesterol efflux pathways and enhanced cholesterol accumulation in HSPCs drive myelopoiesis in a cell-intrinsic fashion[99,121]. Major players in the cellular cholesterol efflux are apolipoprotein E (ApoE) and the ATP-binding cassette transporters ABCA1 and ABCG1[121]. The latter are upregulated in pro-resolving macrophages upon efferocytosis dependent on transcription factor LXR and contribute to inflammation resolution programs[122,123]. Cholesterol accumulation in HSPCs due to double deficiency of ABCA1 and ABCG1, or due to ApoE deficiency, results in HSPC expansion and myeloid differentiation, and hence peripheral monocytosis and neutrophilia[99,124]. The underlying mechanism involves membrane alterations associated with enhanced intracellular cholesterol and elevated cell-surface expression of the lipid raft-associated IL-3Rβ (CD131), which facilitates enhanced IL-3- or GM-CSF-dependent signaling for inducing myelopoiesis[99,124] (Fig.3). A similar mechanism, involving enhanced cholesterol accumulation and lipidomic membrane remodeling that augment CD131-dependent signaling in HSPCs leading to their myeloid differentiation operates in β-glucan-induced trained immunity in HSPCs[98]. Together, immunometabolic adaptations of hematopoietic progenitor cells to inflammatory signals may be the common denominator between the modes of action in trained innate immunity and cardio-metabolic disease. In addition, (mal)adaptive training of hematopoietic progenitor cells may provide a mechanistic basis for comorbidities, such as the enhanced risk of cardiovascular complications in patients with rheumatoid arthritis, periodontitis or other autoimmune or inflammatory disorders[125,126].

The age-associated impairment in HSC function is associated with replication stress[100], while decreased DNA damage response and repair pathways in aged HSCs may promote accumulation of mutations leading to hematological malignancies[127]. Autophagy counteracts the age-associated dysfunction of HSCs by clearing mitochondria, thereby facilitating maintenance of HSC quiescence and regenerative capacity[128]. Aged HSCs display diminished self-renewal and a myeloid bias[129–131]. CD61^{hi} LT-HSCs are highly responsive to inflammatory stimuli and predominate amongst aged LT-HSCs as a myeloid-biased subset regulated by the transcription factors KLF5, IKZF1 and STAT3[131].

The propensity of aged HSCs to accrue mutations and have a myeloid bias and enhanced responsiveness to inflammation may provide a mechanism for clonal hematopoiesis (also known as clonal hematopoiesis of indeterminate potential)[132,133], whose prevalence strongly increases with age and is defined by mutations associated with myeloid malignancies, such as mutations in TET2, DNMT3A and ASXL1, with normal blood counts. People with clonal hematopoiesis have higher risk for hematologic malignancies and cardiovascular disease[132–134]. Consistently, murine deficiency of the epigenetic regulator TET2 results in the expansion of HSPCs with myeloid bias, leading to myeloproliferation[135]. Chimeric Ldlr-deficient mice partially or completely reconstituted with TET2-deficient BM cells have exacerbated atherosclerosis typified by the presence of pro-inflammatory macrophages with enhanced NLRP3-dependent production of IL-1β[133,134]. Clonal hematopoiesis may also accelerate heart failure in an IL-1β-dependent manner[136]. The concept of clonal hematopoiesis could, therefore, integrate aging- and inflammation-related adaptations in myelopoiesis progenitor cells with cardiometabolic inflammation. NLRP3 inflammasome activation is linked to clonal HSPC expansion and progression of the myelodysplastic syndrome (MDS)[137], while IL-6-related inflammation promotes survival of TET2-deficient HSPCs[76], implicating inflammation as a driver of clonal hematopoiesis and MDS.

IL-1β appears as the common denominator of innate immune training in hematopoietic progenitor cells, enhanced myelopoiesis in cardiometabolic disease and clonal hematopoiesis-related exacerbated vascular inflammation. The success of IL-1β blockade (CANTOS trial) in atherosclerosis[138] further supports a major role of IL-1β in these conditions. Moreover, inflammation induced by TLR2 agonists or disseminated bacteria resulting from a disrupted intestinal barrier may promote the progression to pre-leukemic myeloproliferation in TET2-deficiency[139]. Further investigations could elucidate the potential link(s) amongst the aforementioned inflammatory (IL-1β-related) processes, especially trained innate immunity and clonal hematopoiesis, as they appear to participate in a self-sustained vicious cycle, wherein inflammatory disease and inflammatory adaptations of hematopoietic progenitors engage in reciprocally reinforced interactions.

Conclusions

The ability of hematopoietic progenitor cells to sense and adapt to inflammatory stimuli renders them central players in the context of acute peripheral inflammation or infection[1,2]. During infection, HSPCs react to TLR ligands, inflammatory cytokines, including IL-1 or IFNs, and growth factors. Such inflammatory signaling in HSPCs can drive their expansion and myelopoiesis, but may also cause HSPC exhaustion, if chronically sustained[2]. With the

exception of chronic cardio-metabolic diseases[27,103], the role of hematopoietic progenitors cells as central determinants of the host response in chronic diseases has been underappreciated. In cardio-metabolic disease (and possibly other chronic disorders), the adaptation to inflammation that drives myelopoiesis in HSPCs generates a destructive feed-forward loop (Fig.4), in which increased numbers of inflammatory myeloid cells enhance inflammation, which in turn perpetuates HSPC-mediated myelopoiesis[27,103,111,112,116,121]. Importantly, previous infectious or inflammatory challenges can epigenetically imprint an "inflammatory memory" in hematopoietic progenitor cells[97,98,117], thereby contributing to trained immunity. As innate immune training facilitates cardiovascular inflammation[117], it is intriguing to hypothesize that the development of clonal hematopoiesis, which is associated with higher cardio-metabolic inflammation[132–134], might be linked with selective pressure for inflammatory memory[96–98]. A major question is whether adaptation of hematopoietic progenitors to inflammation can provide a unifying concept where inflammatory stimuli (*e.g.*, infections) and multiple risk factors (*e.g.*, obesity, dyslipidemia, psychosocial stress) can be integrated in a meaningful manner to better understand the pathogenesis of different forms of chronic inflammatory diseases or even malignant disorders. This challenging concept needs to be addressed by interdisciplinary studies bringing together experts in immunology, hematopoiesis, metabolism, cardiovascular medicine, as well as mathematical modeling, which could potentially lead to new risk assessment scores for chronic inflammatory diseases.

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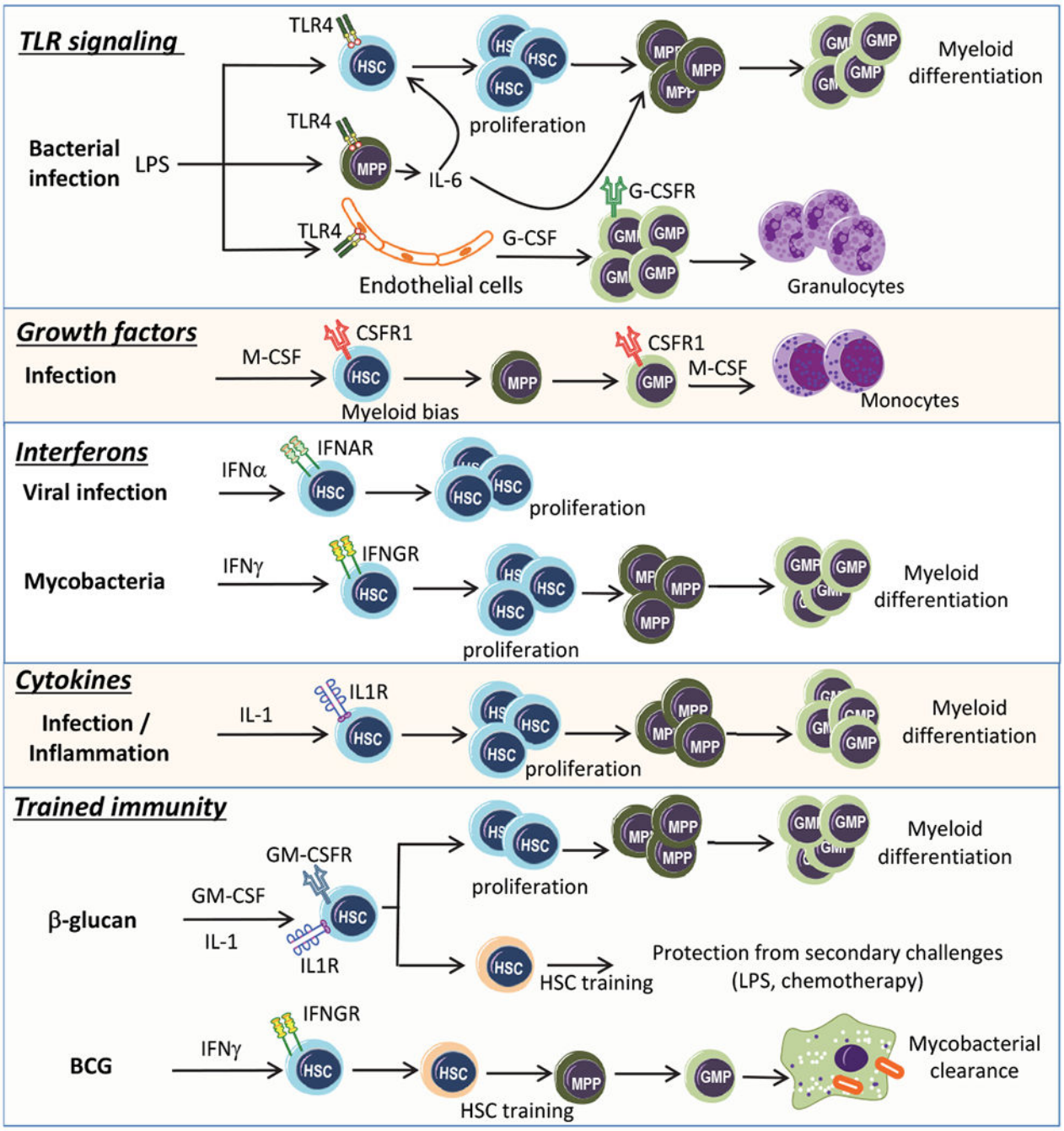

Figure 1. Inflammatory adaptation of hematopoietic progenitors.

Hematopoietic stem cells (HSC) and multipotent progenitors (MPP) express Toll-like receptors (TLR) sensing directly pathogen-derived products, such as LPS, which can drive HSC proliferation[31]. LPS also stimulates release of cytokines, such as IL-6, from MPPs; IL-6 acts in a paracrine manner to promote HSC proliferation and enhanced myelopoiesis[30]. In parallel, LPS stimulates release of G-CSF from endothelial cells[38]. G-CSF acts on myeloid progenitors, especially on granulocyte macrophage progenitors (GMP) driving their differentiation towards granulocytes. In the course of infection, M-CSF can act direcly on

HSCs, promoting their myeloid differentiation[53], and on GMPs to promote monocyte generation[51]. IFN-α, produced in response to viral infections, induces HSC cell-cycle entry at the expense of their self-renewal potential[55]. IFN-γ, produced in the course of mycobacterial infection, results in HSC proliferation and their instruction towards the myeloid lineage[64]. Release of IL-1 during infection or inflammation drives proliferation and myeloid differentiation of HSCs[18]. Trained immunity induced by β-glucan drives the proliferation and sustained myeloid bias in HSCs through IL-1 and GM-CSF. Trained immunity mediates a beneficial response of HSCs to secondary challenges, such as chemotherapy and LPS administration[98]. Additionally, trained immunity induced by BCG reprograms HSCs resulting in the generation of macrophages with enhanced anti-mycobacterial properties[68].

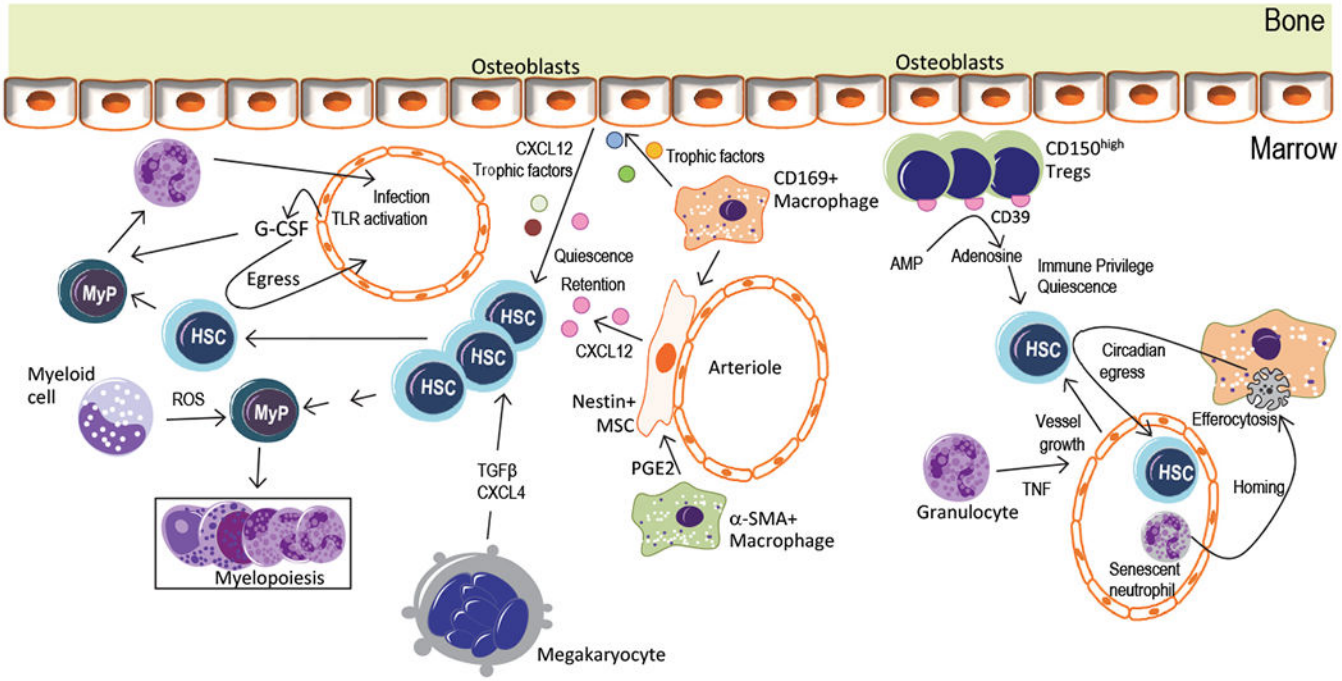

Figure 2. Regulation of HSCs by their progeny in the BM niche.

Innate and adaptive immune cells in the BM, as well as other HSC progeny, such as megakaryocytes, contribute to HSPC adaptation to inflammatory stimuli derived from systemic infection or inflammation. G-CSF, produced by endothelial cells in response to LPS or systemic infection, acts on myeloid progenitors (MyP) stimulating emergency granulopoiesis[38,39] and promotes the egress of HSPCs from the BM[45]. $CD169^+$ macrophages in the BM niche interact with osteoblasts or $nestin^+$ perivascular cells and control their expression of HSC-trophic factors, including CXCL12, which contributes to HSC retention in the niche[85,86]. $CD169^+$ macrophages phagocytose apoptotic neutrophils which, upon senescence, home back to the BM; this process promotes the circadian egress of hematopoietic progenitors into the circulation[88]. α-SMA^+ macrophages secrete PGE2, which acts on $nestin^+$ cells, which in turn secrete CXCL12, thereby contributing to HSC quiescence and retention[87]. In response to systemic infection or inflammation, $Gr1^+$ myeloid cells in the BM release ROS, which stimulates the expansion and differentiation of MyPs, thus contributing to demand-adapted myelopoiesis[89]. Moreover, under inflammatory conditions, granulocytes in the BM can secrete TNF, which stimulates vessel growth and thus indirectly promotes HSPC regeneration[90]. $CD4^+CD25^+FoxP3^+$ T_{reg} cells accumulate on the endosteal BM niche and confer immune privilege to the HSC niche. $CD150^{hi}$ T_{reg} cells support HSC quiescence and engraftment via ectoenzyme CD39-generated adenosine[95]. Megakaryocytes control HSC quiescence through TGFβ1 or CXCL4 signaling[91,92].

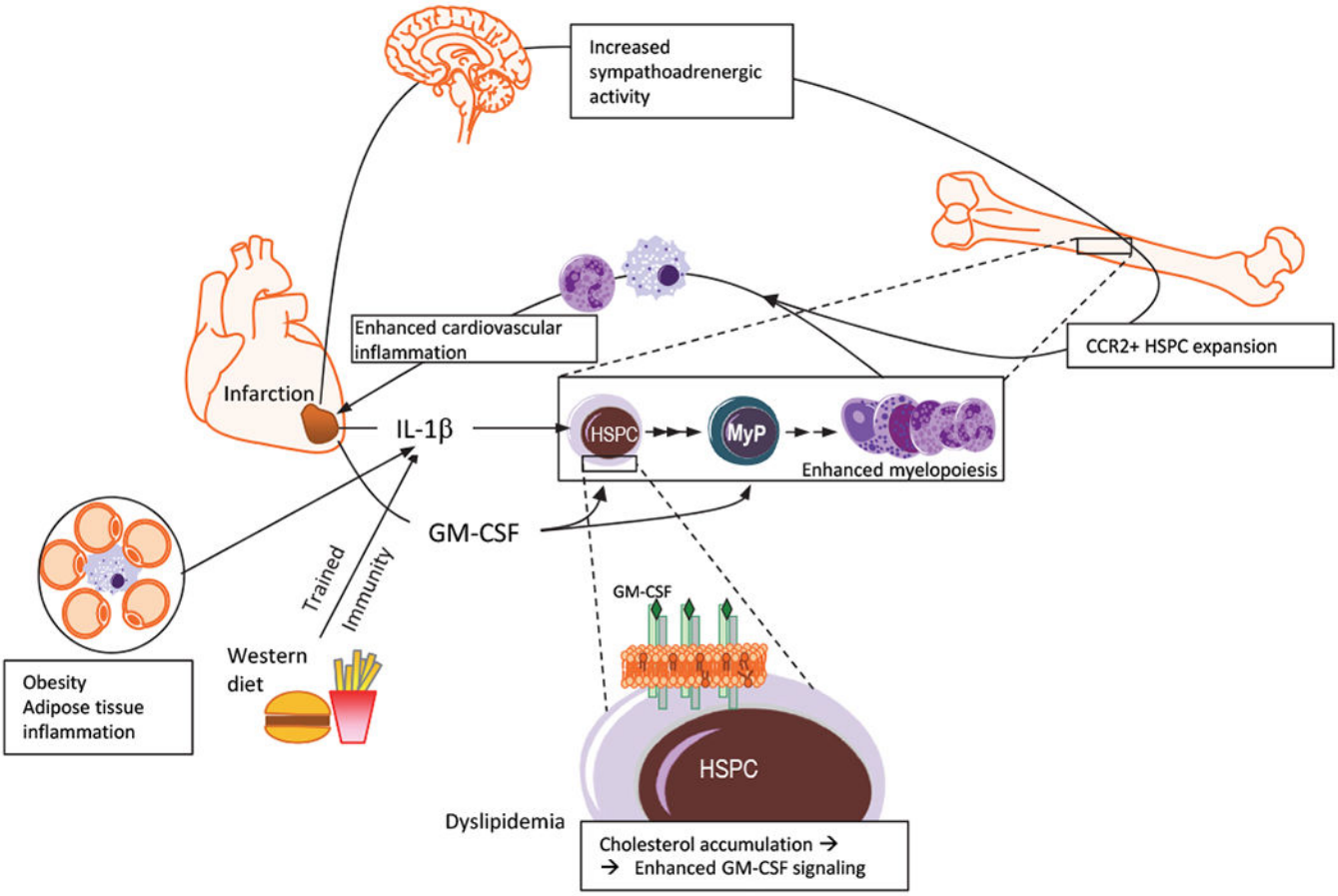

Figure 3: Adaptation of hematopoietic progenitors in cardio-metabolic disease.

IL-1β can act directly on hematopoietic stem and progenitor cells (HSPCs) and is a crucial mediator promoting myelopoiesis under different cardio-metabolic settings like post-myocardial infarction MI, obesity and western-type diet[106,115–117]. Moreover, in MI, increased sympathoadrenergic activity (*e.g.*, due to pain or anxiety) causes expansion and enhanced egress from the BM of HSPCs, including a subset of $CCR2^{+}$ HSPCs, further contributing to enhanced myeloid cell output[111,112]. This enhanced generation of inflammatory myeloid cells may aggravate inflammation and interfere with tissue healing in the case of MI and perhaps in other inflammatory conditions. GM-CSF produced post-MI (or under other inflammatory disorders) promotes myelopoiesis by acting on HSPCs or myeloid progenitors (MyP)[41,118]. Cholesterol accumulation in HSPCs (*e.g.*, due to dyslipidemia or hypercholesterolemia) causes membrane changes associated with enhanced IL-3 or GM-CSF-dependent signaling that induces myelopoiesis[99,124]. Such immunometabolic changes resulting in GM-CSF-dependent enhanced myelopoiesis are also associated with trained immunity-induced IL-1β[98] and may, at least in part, explain why innate immune training aggravates cardiovascular inflammation[117].

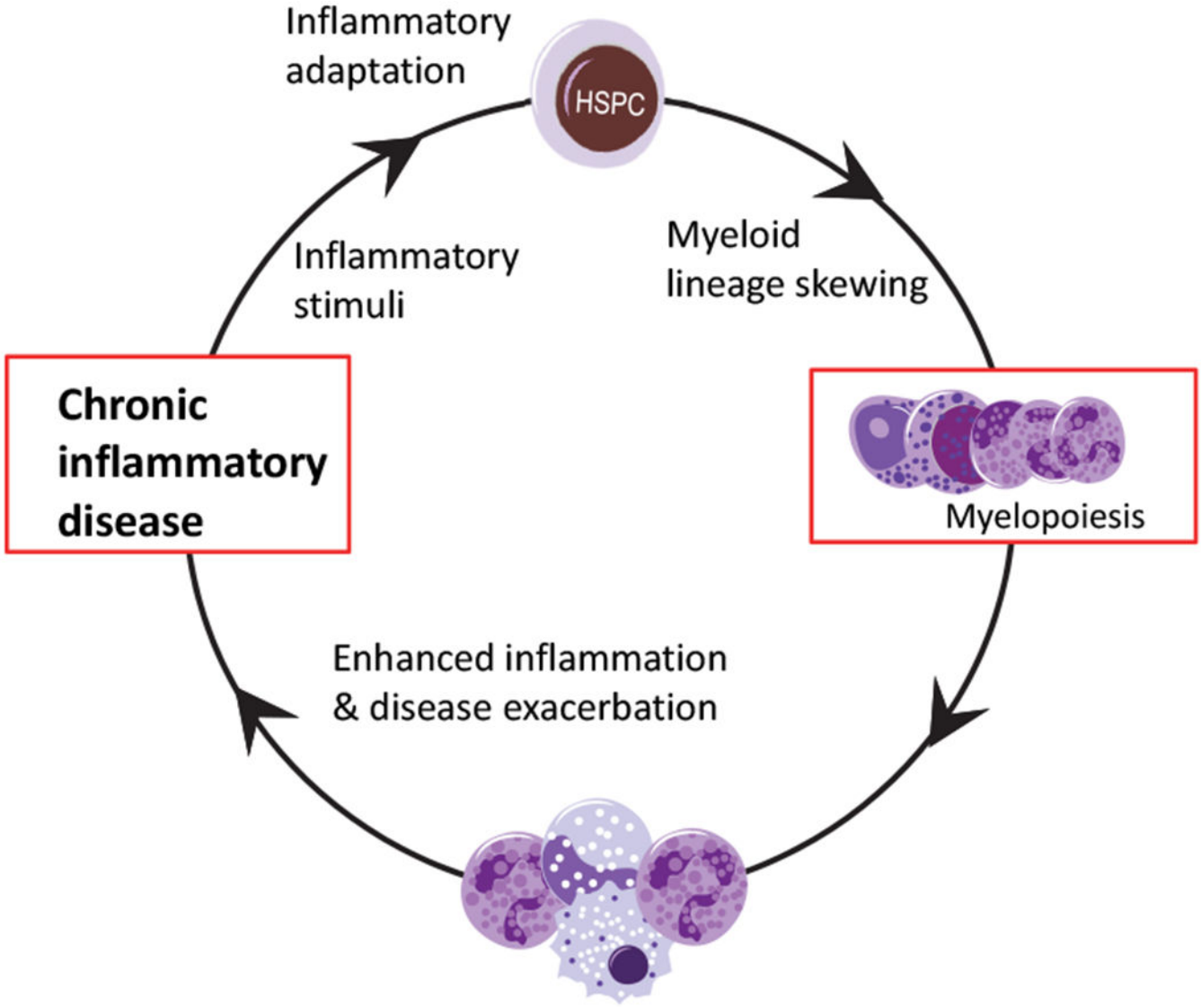

Figure 4. Detrimental feed-forward loop linking HSPC inflammatory adaptation to chronic inflammatory disease.

The ability of HSPCs to sense and adapt to inflammatory stimuli may have detrimental consequences in the setting of chronic inflammatory diseases. According to this hypothesis, the adaptation of HSPCs to inflammatory signals derived from on-going chronic inflammatory disorders (*e.g.*, cardio-metabolic disease) promotes myelopoiesis and output of inflammatory myeloid cells, which in turn further enhance inflammation. This not only can exacerbate the disease but also perpetuate HSPC-mediated myelopoiesis. Thus, a feed-forward loop between inflammation-adapted hematopoietic progenitors and the inflammatory disorder is generated that may contribute to or underlie the chronicity of the disorder.