



Common Sources of Inflammation and Their Impact on Hematopoietic Stem Cell Biology

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Abstract

Purpose of Review Inflammatory signals have emerged as critical regulators of hematopoietic stem cell (HSC) function. Specifically, HSCs are highly responsive to acute changes in systemic inflammation and this influences not only their division rate but also their lineage fate. Identifying how inflammation regulates HSCs and shapes the blood system is crucial to understanding the mechanisms underpinning these processes, as well as potential links between them.

Recent Findings A widening array of physiologic and pathologic processes involving heightened inflammation are now recognized to critically affect HSC biology and blood lineage production. Conditions documented to affect HSC function include not only acute and chronic infections but also autoinflammatory conditions, irradiation injury, and physiologic states such as aging and obesity.

Summary Recognizing the contexts during which inflammation affects primitive hematopoiesis is essential to improving our understanding of HSC biology and informing new therapeutic interventions against maladaptive hematopoiesis that occurs during inflammatory diseases, infections, and cancer-related disorders.

Keywords Hematopoiesis · Pro-inflammatory cytokines · Infectious diseases · Bone marrow · Inflammatory conditions

Introduction

Hematopoietic stem cells (HSCs) are the most primitive hematopoietic population resident in the bone marrow (BM). Although a very rare population, HSCs are the foundation of the hematopoietic tree. Through self-renewal and differentiation into other progenitor populations, HSCs have the unique ability to completely regenerate the blood system after transplantation and thus have been the focus of heavy study for many decades. HSCs are also the foundation of many hematological disorders and pathologies, since any mutation that occurs in an HSC will be passed to downstream blood

lineages. Therefore, it is of critical importance to understand the myriad processes that directly or indirectly affect HSC biology.

HSCs were long perceived to be a population protected from external signals, but recent overwhelming evidence has shifted that view [1••]. For instance, inflammation is now well recognized to have an important influence on HSC function [2••, 3•]. Many types of endogenous and exogenous factors, ranging from mechanical/thermal stimuli to pathogens or aging, induce local or systemic inflammation, and each of these has the potential to affect HSC activity. The aim of this review is to summarize the pro-inflammatory mediators and sources of inflammation known to affect HSC biology.

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Pro-inflammatory Cytokines

Cytokines (cyto, from Greek “κύτος” kytos “cavity, cell” + kines, from Greek “κίνησις” kinēsis “movement”) are small proteins (5–20 kDa) that signal between cells and in many cases can mediate inflammatory responses. Cells with innate receptors sense a range of inflammatory insults (i.e., tissue damage, infection) and in response produce pro-

inflammatory cytokines to recruit immune cells to clear the damage.

HSCs express toll-like receptors (TLRs) that recognize pathogen-associated molecular patterns (PAMPs) and can therefore directly sense pathogens [1••, 4•]. Critically, on their membrane, HSCs also express cytokine/growth factor receptors that are able to sense pro-inflammatory mediators secreted by other cells [1••]. Though the role of pro-inflammatory cytokines on HSC regulation is well known and widely accepted as a key factor of HSC biology [1••, 2••], the physiological relevance of direct sensing and responses to pathogens (by being infected or the recognition of PAMPs) by HSCs remains unclear [4•, 5•]. Specifically, the consequences of inflammation on HSC persistence, clonal evolution, differentiation, and function remain the subject of current investigations.

Distinguishing between the acute and chronic effects of pro-inflammatory cytokines on HSC function represents another layer of complexity. While short-term induction by a range of cytokines such as IFN γ , IFN α/β , IL-1, TNF α , or IL-6 (Table 1) increases proliferation, long-term exposure to these same cytokines can damage HSC function [2••]. Recently, the impact of pro-inflammatory cytokines on HSCs has been thoroughly reviewed [2••], as summarized in Table 1. The impact of inflammatory cytokines on the HSC niche has also been reviewed recently [3•, 6].

The sources of pro-inflammatory cytokines that affect HSC function range widely, from acute and chronic infections to radiation injury and autoinflammation (Table 1). These sources of inflammation and conditions in which they affect HSC biology are the main focus of this review.

Sources of Inflammation

Infectious Diseases

Bacterial Infections

Mycobacterial infections are associated with bone marrow suppression, perhaps because of their chronicity and capacity to invade the bone marrow. Our group had shown that mycobacterial infections such as those mediated by *Mycobacterium avium* promote HSC proliferation in an IFN γ -dependent manner [7••], ultimately depleting HSCs due to terminal myeloid differentiation promoted by the transcription factor Batf2 [8•, 9]. Similarly, chronic *Mycobacterium tuberculosis* (Mtb) infection drives IFN γ production in CD4 T cells, thus disrupting hematopoietic homeostasis [10]. Moreover, Choi et al. demonstrated during Mtb infection in mice that HSPC proliferation is associated with increased TNF α and IL-6 signaling via the toll-like receptor (TLR) pathway [11].

Indeed, HSCs express TLR2 and TLR4 and therefore are able to recognize bacterial cell wall components from Gram-

positive and Gram-negative bacteria, respectively [1••]. Mice exposed to TLR2 and TLR4 antagonists showed increased HSC differentiation and reduced self-renewal capacity [4•, 12•]. LPS, a TLR4 agonist, affects HSC function through TLR4-TRIF-ROS-p38 signaling [4•]. A single dose of LPS increases the BM serum levels of IL-1 β , IL-1 α , and CXCL9 [13]. Chronic low-dose LPS administration increases HSC proliferation and myeloid differentiation and functionally impairs HSCs, as shown by their reduced repopulation capacity in serial transplantation experiments [14•, 15]. Sonic Hedgehog (SHH) signaling has also been shown to play a role in HSPC activation during *Escherichia coli* infection [16].

Using a mouse model of an emerging tick-borne disease carried by the lone star tick *Amblyomma americanum*, infection by the Gram-negative bacterium *Ehrlichia muris* was shown to suppress BM function and myelopoiesis in an IFN γ -dependent manner [17–20]. Moreover, Smith et al. demonstrated that during *E. muris* infection, IFN α/β signaling also induces BM suppression, leading to emergency myelopoiesis and reduced hematopoiesis. Consistent with this, *Ifnar1* null mice had increased hematopoiesis and maintained HSC functions despite infection with *E. muris*. Mechanistically, it has been reported that type I IFNs induce loss of HSPC via RIPK1-dependent cell death during *E. muris* infection [21].

In Gram-positive *Staphylococcus aureus* infection, HSPCs are stimulated by IL-1 β traffic to the infection site, where they are activated via TLR2/MyD88 and produce prostaglandin E2 (PGE2) to promote granulopoiesis [22•, 23]. Another study showed that treatment with TLR2 agonist PAM3CSK₄ caused HSC expansion but loss of their BM repopulating activity; these effects were partially mediated by G-CSF and TNF α [12•].

Viral Infections

Viral infections, including parvovirus [24, 25], HIV [26], viral hepatitis [27], Epstein-Barr virus [28]), and influenza [29], are often associated with BM suppression due to increased production of pro-inflammatory cytokines [30]. Our group has shown that interferons released during LCMV infection promote cell division and myeloid differentiation of HSPCs [9]. Though both type I and type II interferons are induced during LCMV infection, effects on HSPCs were especially dependent on type II interferon. Similarly, vesicular stomatitis virus (VSV) and murine cytomegalovirus (MCMV) infections activate LT-HSC independently of type I interferon receptor signaling [31•]. Therefore, strong evidence in LCMV, VSV, and MCMV virus models showed that type II interferon but not type I interferon is necessary for HSPC activation. Non-acute MCMV infection induces a sustained inflammatory milieu within the BM that is associated with long-lasting impairment of LT-HSC function, even when the virus is cleared from BM

Table 1 Cytokines, growth factors, and pathways/transcription factors involved in HSC function and their different inflammatory sources

Growth factor/ inflammatory cytokine	Sources of inflammation	Main effects on HSCs	Pathways/transcription factors in HSCs
G-CSF	Bacterial infections, cancer, autoimmune disease [58]	Emergency granulopoiesis [118], proliferation [119], mobilization [120]	G-CSFR-STAT3-C/EBP β [77, 118], C/EBP α [121]
GM-CSF and M-CSF	Bacterial infections, cancer	Emergency granulopoiesis [121], extramedullary myelopoiesis [123], <i>trained immunity</i> [124], monocyte differentiation [125]	SOCS3 (negative regulator) [122] G-CSFR [126] PU.1 [125]
IFN type II	Acute and chronic bacterial and virus infections (mycobacteria [7•, 8•], LCMV [127]), fungi infections [53], clonal hematopoiesis [128], aplastic anemia [129], liver cirrhosis [130], HLH disorder [131, 132], cancer [133], autoimmune disease [58]	Proliferation [7•, 127], impaired self-renewal capacity, secondary stress-induced apoptosis [8•], myeloid differentiation [9], <i>trained immunity</i> [134]	IFNG receptors and Stat1 [7••] Batf2 in terminal differentiation [8•]
IFN type I	Bacterial [21] viral infections, fungi infections [53], cancer, DNA-stimulated cell death [135]	Proliferation (short term), impaired HSC repopulation capacity (long term) [136], impairment and attrition [137], apoptosis [21], stimulate proliferation and post-transcriptional protein synthesis in a primed subpopulation of stem cell-like megakaryocyte-committed progenitor [138]	IFN- α/β receptor and STAT1 [136] IRF2 (negative regulator) [139], IRF3 [140] Reduction expression involved in cell quiescence (p27, p57, Foxo1, Foxo3, Pten) [141] ROS-production in DNA damage [137] NFAT5 (negative regulator) [140] TLR4 [14•], NOD1/2, Myd88-TRIF-ROS-p38 [4•] RIPK2- NF- κ B-MAPK [143] C/EBP β [142] <i>TNFα production required for PU.1 induction by LPS</i> [145], NFKB, CXCR4, HDAC5
LPS	Gram-negative bacterial infections (i.e., <i>E. coli</i> , <i>Salmonella</i> [4•, 14•])	Proliferation, migration [4•], myeloid skewing and halter engraftment capacity [14•], extramedullary hematopoiesis [14•], <i>trained immunity</i> [142]	IL-1R-NF- κ B-PU.1 [148]
TNF α	Bacterial infections, cancer, aging [72], liver cirrhosis [130], autoimmune disease [58], aging [73, 74], neurological disorder [63]	Proliferation, myeloid differentiation, and repopulation capacity [144]. Self-renewal, resistance to TNF α -derived apoptosis	
IL-1	Bacterial infections, cancer [146], wounds [23], DNA-stimulated cell death [135], aging [72], liver cirrhosis [130], autoimmune disease [58, 147], neurological disorder	Proliferation, myeloid differentiation, impaired self-renew (chronic administration) [148], local granulopoiesis [23], <i>trained immunity</i> [124]	
IL-6	Bacterial infections, cancer, aging [71, 72], neurological disorder [63, 64], microbiota [149]	Proliferation and myeloid differentiation [150]	<i>Shp2/Stat3/Morbid</i> [151]

[31•]. Moreover, HIV infection can alter HSPC differentiation via ILR8 signaling [32]. IL-18, a cytokine that induces IFN γ production, protects lymphoid HSPC from apoptosis during primary HIV infection; however, high levels of IL-18 in chronic HIV infection deter lymphoid HSPC proliferation [33, 34]. Of interest, SARS-CoV-2 infection (the virus that causes COVID-19) also produces a dramatic increase in many pro-inflammatory cytokines known to affect HSCs, such as TNF, IL-1 β , IL-6, IL-8, G-CSF, and GM-CSF. This increase occurs especially in patients who are critically ill with COVID-19; therefore, future studies should investigate how this novel coronavirus affects BM/HSC activity [35].

Some miRNAs have been associated with HSC regulation in viral infections [36, 37]. Our group reported that the loss of miR-22, which normally promotes IFN α production during viral infection, is beneficial for mice in a model of LCMV infection. We found that miR-22-null mice had better overall survival and HSC homeostasis than WT mice after LCMV challenge, which can be attributed to their blunted IFN response to infection [37].

Protozoan and Fungal Infections

Plasmodium is a genus of intracellular parasites that cause malaria. Using a mouse model of malaria infection based on natural, sporozoite-driven *Plasmodium berghei* infection, Vainieri et al. showed that HSCs become highly proliferative during infection [38•]. In line with this increase in proliferation, LT-HSC and LMPP numbers were higher as early as day 3 post-infection indicating that critical responses take place in the primitive hematological populations at very early stages of sporozoite infection [38•]. Furthermore, primitive HSCs proliferated significantly at days 7–10 of infection. Given that replication stress has been associated with loss of functionality of aged HSCs [39] and the appearance of pre-malignant hematopoietic conditions such as clonal hematopoiesis [40], results from this study support the long-term consequences of sustained HSC proliferation on HSC fitness.

Toxoplasma gondii (*T. gondii*), the agent of toxoplasmosis, is a widespread intracellular protozoan parasite that infects up to a third of the world's population [41]. Given its overall prevalence, reactivation of toxoplasmosis is a significant side effect among recipients of hematopoietic stem cell transplantation (HSCT) [42]. *T. gondii* infection leads to bone marrow suppression, reducing white blood cells, reticulocytes, and platelets [43]. Mice with *T. gondii* infection showed increased granulopoiesis, leading to increased functional activity of granulocytes in the blood [43]. *T. gondii* GA15 protein has been shown to be involved in the regulation of TNF and NF- κ B signaling pathways using hamster kidney cells in vitro [44] and triggers cGAS/STING signaling in a STING- and TRAF-dependent manner in mice [45]. Since activation of STING is necessary for the production of type I interferons [46] and

TRAF pathways affect primitive hematopoiesis in other models [47], these signaling pathways also may affect hematopoiesis during toxoplasmosis infection in humans.

Fungal infection is often associated with high mortality in HSCT patients [48, 49]. After stem cell transplant, fungal infection, including mucormycosis, can lead to myriad severe complications including invasive fungal sinusitis, emphysematous gastritis, and other invasive fungal infections associated with extremely high mortality [50, 51]. Mucormycosis is commonly found in hematological patients, according to a review of 929 reported cases by Roden et al. [52]. Although it has been reported that IFN γ signaling directly activates antifungal responses in neutrophils [53], we found no evidence that *Aspergillus fumigatus* infections affect HSC function (data not published); further research is warranted to deepen our knowledge in this area.

Chronic Inflammatory/Autoimmune Diseases/Neurological Diseases

Abnormal and steady elevation of serum pro-inflammatory cytokines such as IL-6, TNF α , IL-17 α , GM-CSF, and G-CSF that potentially affect HSC function is a hallmark of chronic inflammatory and autoimmune diseases. Chronic intestinal inflammation, driven by abnormal IL-23-dependent responses, causes increased proliferation of HSPCs, which accumulate at extramedullary sites. Eosinophil activation by GM-CSF, which promotes eosinopoiesis in synergy with IL-5, is responsible for this dysregulated hematopoiesis [54•, 55]. Niu et al. have shown in a lupus mouse model that HSCs expanded with an increased capacity for self-renewal due to a single nucleotide polymorphism in the *cdkn2c* gene, leading to downregulation of p18^{INK4c} [56•]. Moreover, in patients with atherosclerotic cardiovascular disease (CVD), HSPCs have higher proliferative capacity than healthy individuals [57]. Chronic inflammation also is associated with autoimmune diseases such as rheumatoid arthritis (RA). In one recent report using a mouse model of human RA, Hernandez et al. showed that HSCs in RA mice persist in a quiescent state, consistent with the activation of proliferation arrest genes despite the increase of inflammation and myeloid production. Treating RA mice with inflammatory cytokine blockade normalized hematopoiesis and attenuated myelopoiesis [58]. Some monogenic autoimmune disorders such as IPEX syndrome and Stat1 gain-of-function are characterized by excessive inflammation and disordered hematopoiesis [59, 60]. With increasing evidence suggesting chronic inflammation disrupts HSC functions, HSCT has become a viable option to treat patients with such severe chronic inflammatory and autoimmune diseases [61].

In addition to traditional autoimmune diseases, people with neurological disorders including depression have been shown to present with higher serum levels of TNF α , IL-6, IL-13, IL-

18, IL-12, IL-1RA, and sTNFR2, as well as decreased IFN γ [62–64]. Mechanistically, activation of microglia through PAMPs or danger-associated molecular patterns (DAMPs) signaling promotes inflammatory responses in neurological disorders such as Alzheimer's disease, frontotemporal dementia, and Parkinson's disease [65]. Since many of the cytokines associated with neuroinflammation are also involved in HSC regulation (Table 1), it is reasonable to speculate that people with neuroinflammatory disorders could have BM/HSC abnormalities. Interestingly, neurotrophic factor receptor RET plays a role in promoting HSC survival and expansion by activation of p38/MAP and CREB through Bcl2/Bcl2l1 [66]. Moreover, HSC quiescence is regulated by Schwann cells—a type of glia wrapping nerve fibers in the BM—through TGF- β signaling, suggesting that glial cells may maintain HSC hibernation by regulating activation of latent TGF- β within the BM niche [67]. Due to the high and increasing prevalence of these disorders, new studies are needed to reveal the plausible relationship between inflammation, neurological diseases, and HSC function.

Aging

Many alterations that occur in the aging hematopoietic compartment are common to inflammatory processes [3•, 68], including (1) myeloid bias in hematopoiesis with a shift in the frequency of CD150+ high HSCs [69], (2) accumulation of DNA damage [70], and (3) increased basal levels of pro-inflammatory cytokines such as IL-6 [71, 72], TNF- α [73, 74], IL-1R α , and C-reactive protein [3•] in the serum of healthy elderly people. Chronic treatment with a low dose of LPS in mice leads to myeloid skewing [14•] reminiscent of the myeloid skewing that is seen in normal aging. A recent report linked the activity of retrotransposable elements (RTE) with sterile inflammation to aging. During cellular senescence, LINE-1—the only human RTE capable of autonomous retrotransposition—became transcriptionally derepressed and activated an IFN-I response, which further contributed to the maintenance of the senescence-associated secretory phenotype [75]. Environmental factors including inflammation are also important in the progression of age-associated clonal hematopoiesis [76•], as shown by high levels of IFN γ in the serum of patients with *DNMT3A*-related clonal hematopoiesis and ulcerative colitis [77]. Collectively, these studies reveal a clear interplay between low-grade inflammation and aging and suggest that the hematopoietic changes seen with age are attributable at least in part to inflammation.

Chemotherapy and Radiation

Under the stress caused by exposure to cytotoxic chemotherapy, HSCs are activated and enter the cell cycle, which drives emergency myelopoiesis and rapid regeneration of the

hematopoietic system. Moreover, radiation including X-rays and γ -rays induce DNA damage, reactive oxygen/nitrogen species, ER stress, and hypoxia, triggering inflammatory responses and increased production of pro-inflammatory cytokines, such as IL-1 α , IL-1 β , IL-12p40, TNF- α , and IFN γ [78]. Radiation can also lead to genetic changes in HSCs [79]. Rodman et al. reported that exposure to chronic solar energetic particles (SEP) and galactic cosmic ray (GCR) radiation can cause mutations in genes involved in hematopoiesis, modulate the engraftment as well as lineage commitment of HSCs, damage BM stromal cells and thus disrupt the niche, and contribute to the development of abnormal T-ALL [80•, 81].

Gender

Physiological differences between women and men play a prominent role in their exposure to infectious diseases and the frequency and manifestations of autoimmunity, including autoimmune diseases [82]. It is widely accepted that men are more susceptible to infections (i.e., tuberculosis and parasites), while women present with more autoimmune diseases [82]. Estrogen and testosterone differentially regulate inflammation [83]. Powell et al. revealed that estrogen increased inflammation in a model of human knee joint injury, while testosterone reduced inflammation at the site of injury [83]. Sex hormones regulate the transcription of many genes involved in immune cell development and maturation, regulation of immune responses, and modulation of immune signaling pathways; however, few reports have studied the direct effect of sex hormones on HSC regulation [82]. Nakada et al. showed that estrogen can induce more frequent HSC division in females compared with males through its interaction with estrogen receptor-alpha on HSCs [84••]. Indeed, this study showed estradiol treatment increased HSC division in male mice.

Lifestyle Factors Can Affect HSC Inflammation

Dietary

Metabolic disorders including atherosclerosis, obesity, and type 2 diabetes are characterized by the presence of a chronic inflammatory state that negatively affects the regulation and function of HSCs and progenitors [85]. Therefore, human behaviors/actions to reduce those deleterious, chronic sources of inflammation are vital to improve HSC function. It has been reported that the ability for HSCs to self-renew and proliferate depends on metabolism [86–88]. While fasting appears to enhance HSC function, a number of recent reports have found that high-fat diets (HFDs) and obesity reduce HSC activity. HFDs are associated with increasing inflammation in the central nervous system, liver, adipose tissue, skeletal muscle, and

intestine [89]; alter the microbiome; increase the level of LPS; and promote production of pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF- α [90]. Accumulation of cholesterol in innate immune cells [91] and HSPC [92] promoted increased inflammatory responses through the TLR signaling pathway [91] and increased myelopoiesis by amplifying Janus kinase 2 (JAK2) signaling [92]. Indeed, inhibition of JAK2 reduced atherogenesis by suppressing myelopoiesis [93].

Vitamins are essential nutrients for human health. Taya et al. showed that valine amino acid plays an important role in the maintenance of HSC and BM niche [94]. In a recent report, vitamin B₆ intake reduced the number of inflammatory markers, such as C-reactive protein, IL-6 receptor, and white blood cell count as well as overall inflammation score [95]. Vitamin C alleviates inflammation by decreasing the level of IL-6, fasting blood glucose, and high-sensitivity C-reactive protein [96], and regulates HSPC self-renewal by acting as a co-factor for TET2 by driving DNA hypomethylation. Vitamin D treatment has also been shown to promote colony formation by HSPCs [97].

A healthy diet is associated with increased survival and lower risks of chronic health conditions in HSCT patients [98]. In line with this, a diet rich in n-3 PUFA-rich fish oil promotes hematopoiesis in the bone marrow and spleen of mice, mediated in part by MMP12, and may induce myeloid-derived suppressor cell differentiation to suppress tissue inflammation [99]. Additionally, a number of studies support the idea that fasting/dietary restriction plays an important role in prolonging a healthy lifespan by regulating inflammatory responses and HSC function [100•, 101]. Cheng et al. showed that 48-h cycles of fasting promoted HSC regeneration in mice by inhibiting insulin growth factor 1 (IGF1) signaling [100•]. Diabetes is also seen as fasting-like state. A retrospective analysis of HSCT patients found that diabetes negatively correlated with donor HSPC mobilization [101].

Exercise

Frodermann et al. reported that exercise modifies HSPC function by reducing leptin signaling in the bone marrow niche [102••]. Specifically, physical activity can protect mice from chronic leukocytosis by reducing hematopoietic activity without compromising emergency hematopoiesis. Exercise attenuates the production of leptin in adipose tissue, which in turn enhances CXCL12, a quiescence-promoting hematopoietic niche factor important in the maintenance of HSC function [102••]. In a separate study, mice fed a high-fat diet without exercise showed increased common myeloid progenitor cells and BM inflammation [103]. Overall, these studies indicate that exercise maintains HSC function by decreasing inflammation within the BM niche.

Smoking

Mice exposed to cigarette smoke exhibited increased extramedullary hematopoiesis in the spleen, inhibition of HSPC homing into BM, decreased mesenchymal stromal cells and HSCs, and increased pro-proliferation genes that lead to the expansion of HSPCs [104–106]. Cigarette smoke extract decreased bone formation but increased an array of different interleukins such as IL-1 β , IL-2, IL-4, IL-5, IL-9, IL-10, IL-12p40, IL-13, IL-17- α , G-CSF, GM-CSF TNF- α , and IFN- γ [107••]. Since many of these cytokines have been shown to impact hematopoiesis, it is reasonable to hypothesize that smoking may significantly affect hematopoiesis by inducing systemic inflammation. In support of these effects, smoking has been identified as one of the factors related to the emergence of clonal hematopoiesis [76•] and hematological cancers [108•].

Microbiome/Antibiotics

Human conditions associated with altered intestinal bacterial populations, such as inflammatory bowel syndrome or prolonged antibiotic use, are associated with adverse hematologic effects, including anemia and neutropenia [109]. Recent studies into these interactions illustrated that microbiota modulate hematopoiesis in the BM [109]. Germ-free mice have fewer HSPCs, abnormal splenic myeloid counts, and impaired T cell function compared with wild-type mice [110, 111, 112••, 113–115]. Our group has shown that mice treated with antibiotics have reduced red blood cells, platelets, and white blood cells in peripheral blood [109, 112••], coupled with decreased HSCs, multipotent progenitors, granulocytes, and B cells in the BM. However, these studies also revealed an increase in the number of CD8+ T cells, suggesting disruption of T cell homeostasis in antibiotic-treated mice could lead to increased inflammation and cause impaired progenitor maintenance [112••]. Mechanistically, Stat1-null mice and antibiotic-treated wild-type mice had similarly low numbers of BM HSPCs and granulocytes. We found that treating Stat1-null mice with antibiotics did not further suppress cell counts, suggesting that STAT1 signaling, stimulated by the microbiota, is required for normal hematopoiesis and providing a clear link between microbiome and inflammatory/interferon pathways [112••].

Indeed, a recent report by Staffas et al. showed the microbiome and antibiotic treatment have an even more profound effect on HSC regulation than previously envisioned. The authors found that gut microbiota induces engraftment of HSPCs following BM transplant, while antibiotic treatment impairs immune reconstitution in the post-transplant setting [116]. Moreover, Lee et al. showed

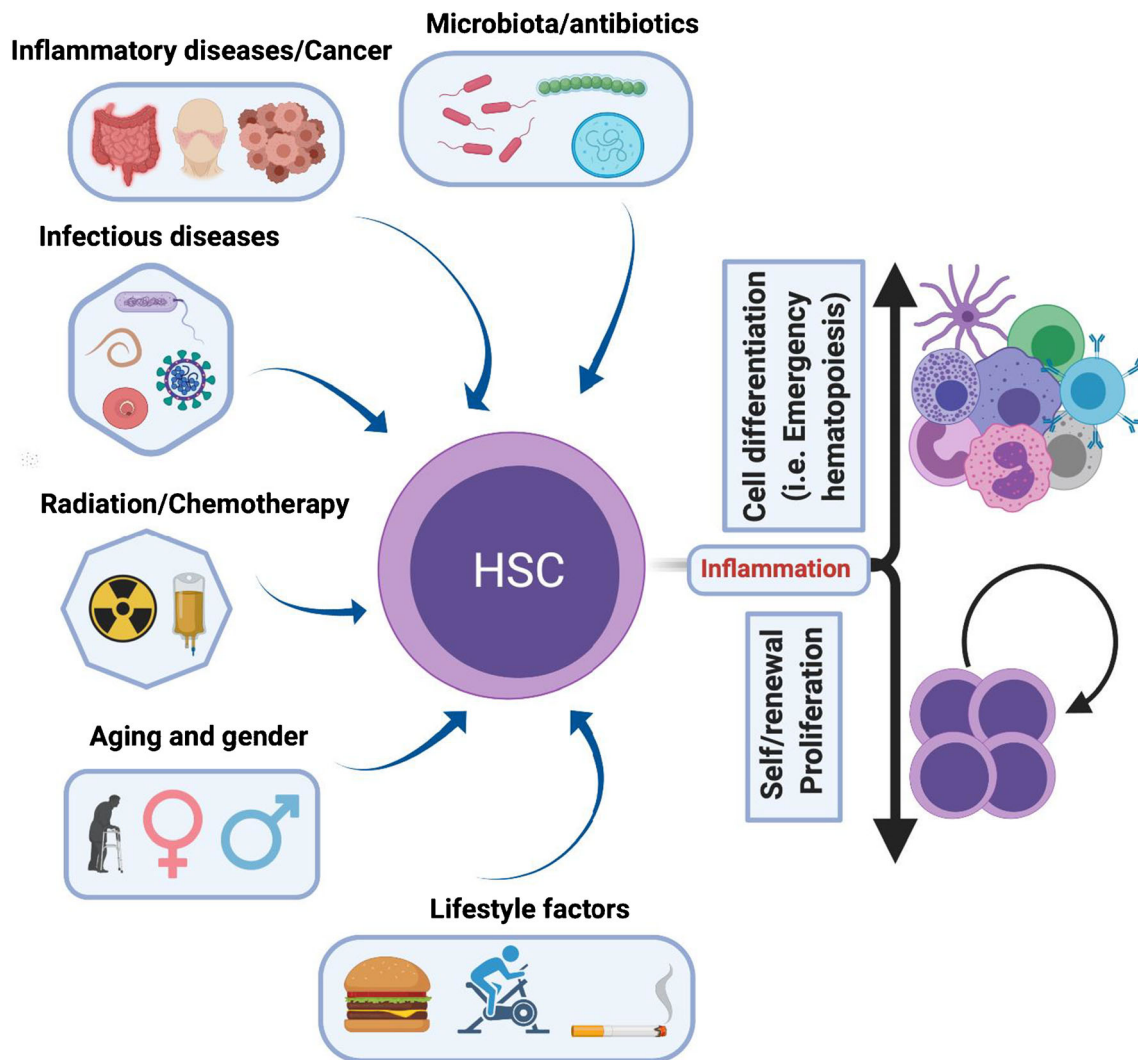


Fig. 1 Main sources of inflammation that affect HSC biology

that microbiota-derived molecules are transported in the BM and recognized by BM CX3CR1+ mononuclear cells to modulate hematopoiesis [117].

Conclusions and Future Directions

In summary, recent work indicates that many different conditions (Fig. 1) produce pro-inflammatory mediators that affect HSC biology. Rather than being inert cells that are isolated and protected from external signals, we now know that HSCs are constantly responding to the shifting inflammatory environment caused by infectious diseases, cancer, gender, aging, radiation, and lifestyle factors (Fig. 1). Inflammation is the immune system's response to harmful stimuli and initiates the healing processes and defense mechanisms vital to health. However, chronic inflammation contributes to a number of diseases and critically damages HSC biology. Since HSCs

are the foundation of all blood cells and any genetic or epigenetic modification is passed from them to downstream populations, it is vital to understand how inflammation disrupts HSCs and blood regulation.

While some inflammatory sources are intrinsic to life (i.e., aging), others can be modulated (i.e., diet, smoking) to improve health. Current evidence demonstrates that a healthy lifestyle can benefit HSC biology and thereby prevent or delay the appearance of pre-malignant conditions and/or hematological disorders fueled by inflammation. Further research is necessary to deepen our understanding of how specific inflammatory insults physiologically alter HSCs and reveal the most effective therapeutic strategies to diminish the deleterious effects of inflammation on BM function.

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Compliance with Ethical Standards

Conflict of Interest Katherine King, Daniel Hormaechea Agulla, and Duy Le declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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