Unexpected role of inflammatory signaling in hematopoietic stem cell development: its role beyond inflammation

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Purpose of review
Inflammatory signaling under pathological conditions like infection and inflammation has been extensively studied. Whether inflammatory signaling plays a role in physiology and development remains elusive. The review summarizes recent advances in inflammatory signaling with particular focus on how distinct inflammatory signaling regulates hematopoietic stem cell (HSC) development. Understanding the underlying mechanism of inflammatory signaling on HSC development may help to generate and/or expand a large number of functional HSCs for clinical application.

Recent findings
Like the hematopoietic progenitors, HSCs can be the first responders to infection. An unexpected observation is that genes involved in innate immunity and inflammatory signaling are enriched in emerging HSCs and their niche during embryogenesis. Thus, inflammatory signaling may also play a role in HSC development in the absence of infection and inflammation.

Summary
Inflammatory signaling is not only an important regulator of HSCs in response to infection, but also plays a previously unrecognized role in HSC development in the absence of infection and inflammation. The baseline inflammatory signaling can be activated to promote HSC development in cell autonomous and noncell autonomous manners. However, direct response of HSCs to inflammatory stimuli is not always advantageous and excessive chronic signaling can have negative effects on HSC regulation and function.

Keywords
hematopoietic stem cell, hemogenic endothelium, inflammatory signaling, Toll-like receptor 4 nuclear factor kappa-light chain enhancer of activated B

INTRODUCTION

Inflammation is a protective response for the body homeostasis which can be triggered by pathogen infection or injury such as trauma and stroke. The hematopoietic system is the foundation for the inflammatory response [1]. Hematopoietic stem cells (HSCs) can produce all types of blood cells and replenish immune effector cells during infection. Apart from myeloid cells such as macrophages and dendritic cells, which are the innate immune cells, endothelial cells [2], and mesenchymal cells [3] also contribute to inflammatory response. In response to inflammatory stimuli, the inflammatory signaling in the innate immune cells is activated to secrete inflammatory cytokines to keep the homeostasis of the hematopoietic system. The inflammatory stimulus, which is called pathogen-associated molecular patterns (PAMPs), recognizes receptors such as Toll-like receptors (TLRs) in the immune cells. Subsequently, the inflammatory response is triggered by inflammatory cytokines including tumor necrosis factor alpha (TNFα), interferons, and interleukin (IL) family members. These inflammatory cytokines recruit immune effector cells to the inflammatory tissues and modify vascular endothelial permeability to initiate the inflammation [4]. Although most previous studies have focused on the function of innate immune cells, recent studies have revealed that inflammatory signaling regulates not

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KEY POINTS

- Inflammatory signaling is activated to stimulate stress hematopoiesis during infection and injury.
- Inflammatory signaling regulates HSPC development during vertebrate embryogenesis.
- Inflammatory signaling interacts with Notch signaling to facilitate HSPC emergence.

only HSC proliferation and differentiation but also HSC emergence during development. In this review, we discuss recent advances in inflammatory signaling, and particularly focus on how distinct inflammatory signaling regulates HSC development during embryogenesis.

CONVENTIONAL INFLAMMATORY SIGNALING

It is well known that TLR class mediates inflammatory responses and innate immunity from fly to mammals [5]. The *toll* genes encode members of the TLR proteins, whose homologue was firstly identified in the *Drosophila*, which is important in establishing the dorsal–ventral patterning during embryogenesis [6]. In 1996, Lemaitre *et al.* [7] demonstrated that Toll plays a pivotal role in the innate immunity by recognizing microbial conserved motifs PAMPs. PAMPs appear to derive mainly from bacteria or viruses. Different TLRs recognize different ligands. For example, TLR4 recognizes lipopolysaccharide, a major cell wall component of Gram-negative bacteria. TLR signaling is evolutionarily conserved from the *Drosophila* to mammals [5].

Tumor necrosis factor and interferons are TLR inducible proteins that mediate inflammatory responses during infection and injury. Upon activation by TLR signaling, nuclear factor kappa-light-chain-enhancer of activated B (NFκB) and activator protein 1 (AP-1) are translocated to the nucleus to induce the expression of cytokine genes, such as tumor necrosis factor, IL-1b, and IL-6 in response to bacteria [8]. Interferons are glycoproteins, which are essential cytokines for host innate immune responses against viral infection [9].

INFLAMMATORY SIGNALING AND STRESS HEMATOPOIESIS

During the systemic infection, the 'emergency' immune effector cells are produced and they mobilize to sites of infection. The hematopoietic precursors, such as common myeloid progenitors and common lymphoid progenitors in the bone marrow and peripheral blood can quickly replenish the consumed immune cells to maintain the homeostasis within the hematopoietic system. Multipotent progenitors and lineage-committed progenitors downstream of HSCs fight against the inflammatory stimuli, whereas long-term HSCs are rare and often maintained in a predominantly quiescent state in the bone marrow.

From previous long-term transplantation experiments, it has been traditionally thought that hematopoiesis is sustained by HSCs. However, using in-situ labeling and a clonal tracking system, recent studies showed, for the first time, that adult hematopoiesis is largely sustained by a large number of long-lived progenitors, rather than classically defined HSCs in an unperturbed system [10,11▪]. The differences between noninvasive fate-mapping and transplantation results have implications for fundamental understanding of HSC biology. HSCs encounter extraordinary stress during engraftment. The different manners under physiological and stress conditions indicate that HSCs also act as the first responders to infection. As a feedback mechanism, inflammatory cytokines produced during infection are also important regulators of HSCs or hematopoietic stem and progenitor cells (HSPCs) themselves. Bacteremia can cause a 10-fold increase in the number of lineage$^-$c-Kit$^+$Sca-1$^+$ cells in the bone marrow [12]. Furthermore, HSPCs can directly respond to bacterial components via the TLR/NFκB axis [13▪]. Similarly, granulocyte-colony stimulating factor (G-CSF), produced by macrophages at the infection site, stimulates aorta-gonad-mesonephros (AGM)-resident HSPCs to activate the C/ebpβ-Nos2a axis to support HSPC proliferation/expansion [14]. Moreover, in response to interferon alpha (IFNα) treatment, HSCs are able to exit G0 and enter an active cell cycle, which are facilitated by increased phosphorylation of signal transducers and activators of transcription 1 (STAT1) and protein kinase B/Akt, increased expression of IFNα target genes, and upregulation of stem cell antigen-1 [15]. In the bone marrow stem cell niche, such property of HSPCs may play an important role in providing a rapid response from the encounter of an infection to the output of myeloid cells.

INFLAMMATORY SIGNALING AND HEMATOPOIETIC STEM CELL DEVELOPMENT

Interestingly, inflammatory signaling may also play a role in HSC development/function in the absence of infection or pathological inflammation. Single-cell proteomics profiling has shown that HSPCs

express TLRs, functional NFκB signaling, and cytokine receptors [13▪]. Furthermore, the engraftment and function of HSCs were significantly impaired in inflammatory signaling deficient mice [16,17].

Aside from the findings in adult HSCs, these well known inflammatory cytokines are also important homeostatic regulators in the embryonic hematopoietic development. Many inflammatory factors, such as IL-3, IL-1β, and G-CSF, have been found to be expressed in the AGM region. IL-3 and IL-1 receptors are expressed in the AGM region when HSCs first emerge in this site. Furthermore, IL-3 [18] and IL-1 receptors [19] mutant embryos are deficient in HSCs. Similarly, zebrafish G-CSF is required for the specification and proliferation of HSCs [20]. Knockdown of *gcsfr* causes a significant decrease of the number of HSCs, whereas overexpression of *gcsf* ligand significantly increases the HSC population along the dorsal aorta. In our previous study, we also reported that miR-142a-3p regulates the formation and differentiation of HSPCs by affecting the inflammatory signaling cascade *irf7-gcsfr* [21▪]. These finding indicate that inflammatory factors can promote the survival and proliferation of HSCs.

In vertebrate embryos, the earliest definitive HSPCs are generated from a group of specialized endothelial cells, hemogenic endothelium (HE) [22], through the endothelial-to-hematopoietic transition [23] in the AGM region. Interestingly, inflammatory signaling has recently been demonstrated to be a key regulator of HE and HSC emergence. The microarray data show that intra-arterial hematopoietic cluster cells and endothelial cells express genes involved in innate immunity and inflammation [24▪▪]. Furthermore, Li *et al.* [24▪▪] found that mouse embryos lacking IFNγ or IFNα signaling display significantly fewer AGM HSPCs. Similarly, knockdown of IFNγ or its receptor IFNGR1 results in the reduced number of emerging HSCs in zebrafish [25▪▪]. In contrast to the previously study, they showed that IFNγ signaling acts through STAT3, not canonical STAT1 in the context of HSC emergence. These distinct downstream molecules likely contribute to the dual roles of IFNγ signaling in HSC specification and differentiation. Consequently, interferons and interleukins are induced when TLR signaling is activated. Simultaneously, we demonstrated that inflammatory signaling regulates HE-derived HSPC development through a conserved TLR4-MyD88-NFκB signaling [26▪▪]. The TLR4 signaling can regulate the Notch activity to promote HSPC emergence. Interestingly, we also showed that *tnfr2* and *gcsfr*, are both required for HSC emergence via a conserved Notch signaling. Most of the previous results depict that Notch signaling is indispensable for definitive hematopoiesis [27,28]. However, the exact relationship between inflammatory signaling and Notch during HSC emergence is still controversial in recent literature [25▪▪,26▪▪,29▪▪].

Sawamiphak *et al.* [25▪▪] reported that HSC defects caused by treatment with a Notch inhibitor, N-[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester (DAPT), could be rescued by interferon overexpression, suggesting that interferon signaling acts downstream of Notch signaling in HSC development. Conversely, in our study, endothelial-derived Notch overexpression efficiently restored the decreased number of *runx1*$^{+}$ cells in the AGM region in inflammatory signaling-defective embryos, suggesting that the endothelial Notch signaling is downstream of TLR4–MyD88–NFκB-mediated inflammatory signaling to control the emergence of HSPCs [26▪▪]. Consistent with our results, Espin-Palazon *et al.* [29▪▪] showed that activation of tumor necrosis factor signaling induces *jag1a* within endothelial cells to promote HSC specification through Notch receptor Notch1a, indicating that Notch functions downstream of tumor necrosis factor signaling to specify the earliest HSCs. Collectively, these findings indicate that the relationship between Notch and inflammatory signaling might be more complicated than previously thought. Further studies on how the direct effector molecules downstream of inflammatory signaling regulate the strength of Notch signaling will shed light on these fundamental questions in HSC development.

Previous studies have demonstrated the cell-autonomous function of inflammatory signaling during HSC development [25▪▪,26▪▪]. However, inflammatory signaling can also act on HSC development in a noncell autonomous manner as reported recently. Espin-Palazon *et al.* [29▪▪] showed that TNFa through TNFR2 activates the Notch and NFκB sign aling in endothelial cells and consequently, endothelial cell-derived NFκB is critical for HSC emergence. In addition, primitive macrophages siting in the AGM niche can remodel the extracellular matrix via metalloproteinase secretion to permit the earliest HSPC mobilization in the establishment of definitive hematopoiesis (Fig. 1) [30▪▪].

Interestingly, recent evidence suggests that inflammatory signaling activation is also involved in production of hematopoietic cells *in vitro*. The AP-1 family (*FOS*, *JUN*) regulates gene expression in response to a variety of stimuli, including cytokines, growth factors, stress, and bacterial and viral infections [31]. Fos combined with GATA binding protein 2 (Gata2), growth factor independent 1B transcription repressor, and ets variant 6 can promote the conversion of mouse fibroblasts into endothelial-

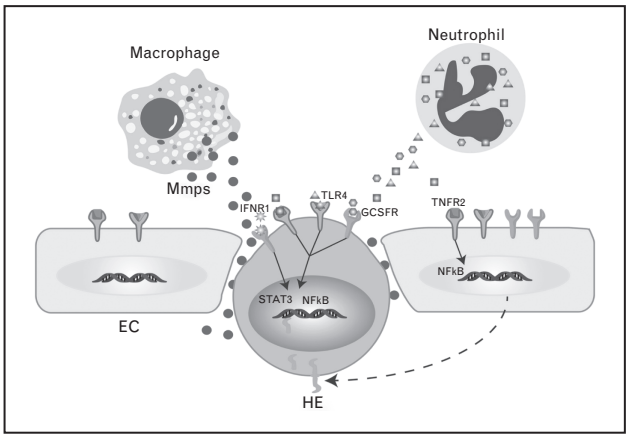

FIGURE 1. Inflammatory signaling during hematopoietic stem cell emergence. TLR4, TNFR2, and GCSFR can activate hemogenic endothelium-derived NFκB signaling, whereas IFNR1 activates STAT3 to promote hematopoietic stem cell emergence. TNFα secreted by primitive neutrophils, through TNFR2, stimulates the endothelial cell (EC)-derived NFκB to activate the Notch1 signaling in hemogenic endothelium (HE). Primitive macrophages remodel the extracellular matrix via secretion of metalloproteinases to permit hematopoietic stem and progenitor cell mobilization.

like precursor cells, which subsequently can be induced into hematopoietic cells [32]. Furthermore, the AP-1 family is reported to be a critical element for induction of hematopoietic program from human pluripotent stem cells [33], suggesting that AP-1 mediated inflammatory signaling might be involved in specifying the hematopoietic fate during the reprogramming process.

PERSPECTIVES

Recently, it has been appreciated that HSCs can respond directly to pathogen infection as well as endogenous ligands for TLR4 and other inflammatory cytokines, which also play a specific developmental role under nonpathogenic conditions surprisingly. Deficient tumor necrosis factor, interferon, or TLR signaling is often associated with HSC defect [25▪▪,26▪▪,29▪▪]. These findings indicate that the baseline inflammatory signaling can be critical for the development and function of HSCs, perhaps by providing just a fine-tuned level of stimulation for initiation of HSC program properly.

An unexpected observation is that innate immunity and inflammatory signaling genes are expressed at the onset of HSC specification during vertebrate embryogenesis, suggesting that the so-called inflammatory signaling may not be just involved in 'inflammatory' conditions, and it may have other roles in development. Recent studies have demonstrated that inflammatory signaling plays an essential role during the earliest HSC emergence through distinct downstream signaling pathways such as Notch and NFκB [25▪▪,26▪▪,29▪▪]. However, there are many open questions remaining. For example, what are the endogenous triggers for the inflammatory signaling that play a developmental role? Extensive studies have reported that many endogenous molecules such as heat shock proteins [34], extra domain A of fibronectin [35], and high mobility group box 1 protein [36] can activate innate immune system via TLR4. These endogenous signals derived from damaged or stressed cells may be the potential endogenous ligands of TLRs [37]. The heat shock protein or the ROS production in apoptosis or hypoxia would be the stress ligands to trigger innate inflammatory signaling. Espin-Palazon *et al.* [29▪▪] show that TNFα is secreted by primitive neutrophils during HSC emergence, in the absence of pathogenic infection. This newly identified mechanism during HSC development may play a crucial role to promote HSPC specification or 'priming'; by doing so, it can provide a rapid response to infection, once in demand.

However, that HSCs can directly respond to inflammatory stimuli is not always advantageous. Excessive immune activation may impair the self-renewal potential and lead to the exhaustion of HSC population [38]. Moreover, inflammatory signaling over-activation has been shown to disrupt HSC function in many autoimmune diseases [39]. Increases in serum levels of inflammatory cytokines, including IL-6, type I IFN, and TNFα and high mobility group box 1, are found in lupus mice. These inflammatory factors can directly promote HSC proliferation and modify HSC functions. Lupus HSCs with enhanced self-renewal capacity may compete out transplanted healthy HSCs, thereby leading to relapses after HSC transplantation [40]. Thus, the tightly-controlled balance of inflammatory signaling to maintain HSC development/function is crucial.

CONCLUSION

Inflammatory signaling is not only an important regulator of HSCs in response to infection, but also plays a previously unrecognized role in HSC development in the absence of infection and inflammation. Understanding the underlying mechanism of inflammatory signaling on HSC development and function will open a new window in HSC biology and may help to generate and/or expand a large number of functional HSCs for clinical application.

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Conflicts of interest

There are no conflicts of interest.

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