

Review

Proinflammatory Signals as
Fuel for the Fire of
Hematopoietic Stem Cell
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Hematopoietic stem cells (HSCs) have the extraordinary ability to both self-renew and generate all mature blood cell lineages. The ability to produce or expand patient-derived HSCs *in vitro* would greatly improve the outcome for patients with blood disorders that are currently treated with allogeneic HSC transplantation. Many laboratories have been working to identify the signals required for HSC emergence in their native environments to apply this knowledge *in vitro*. Recently, several signals traditionally known to underlie classical inflammation have emerged as essential regulators of HSC development. In this review we synthesize the findings that have established inflammatory cues as key regulators of HSC development.

HSC Formation Requires a Complex Cocktail of Molecular Cues, Including Proinflammatory Signals

Stem cells (SCs) are undifferentiated cells with the extraordinary capabilities of both generating many different types of effector cells in a multicellular organism and regenerating themselves. These remarkable traits have led to the extensive study of SCs, with an ultimate goal of utilizing them to repair and replenish damaged tissues in patients. Among all SCs, HSCs are by far the most studied and the only ones utilized routinely in the clinic, for **HSC transplantation (HSCT)** therapies (see [Glossary](#)). Because HSCs are the capstone of the blood hierarchy, they are able to reconstitute the entire hemolymphoid system, making them the perfect tool to treat blood disorders including chronic myeloid leukemia, acute lymphatic leukemia, aplastic anemia, and hemoglobinopathies [1]. HSCs are currently obtained from three sources: bone marrow, peripheral blood, and umbilical cord blood (for a review see [2]). Major challenges facing HSCT are the insufficient number of available HSCs, particularly when the HSC source is cord blood, and **graft-versus-host disease**, which has a high prevalence of 35–60% among all allogeneic HSCT patients with a mortality rate of 50%. *In vitro* generation of high numbers of isogenic HSCs from **embryonic stem cells (ESCs)** or patient-derived **induced pluripotent stem cells (iPSCs)** would thus represent a huge advance in HSCT. However, despite our growing knowledge of intrinsic and extrinsic regulation of HSC biology, HSCs with long-term, multi-lineage functional potential have to date not been generated *ex vivo* [3]. Thus, a better understanding of the full complement of molecular cues required for HSC specification in their native environments is needed to eventually replicate this process *in vitro*.

In vertebrates the HSCs that fuel lifelong production of blood are generated during a brief temporal window in the developing embryo. HSCs derive from a unique endothelial cell

Trends

HSC specification occurs during early stages of embryonic development. A complex network of signals orchestrates this process. Attempts to replicate these signals *in vitro* to instruct embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) to produce *bona fide* HSCs have been unsuccessful to date.

Adult HSCs are armed with immune receptors (TLRs and NLRs) to sense infection and stress signals. They respond with changes in gene expression, producing large amounts of proinflammatory cytokines that contribute to myeloid differentiation and emergency hematopoiesis to fight the cause of infection.

Proinflammatory signals and immune cells are required to specify HSCs in the aseptic embryo. Translational use of these *in vivo* immunomodulators to *in vitro* protocols may improve efforts to generate functional HSCs.

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population lining the floor of the dorsal aorta termed the **hemogenic endothelium (HE)** [4–7]. Studies conducted *in vivo* have identified key requirements for HSC specification, including several classical developmental pathways such as Notch, Wnt, bone morphogenetic proteins (BMPs), and fibroblast growth factors (FGFs) (for a review see [8]). In the past few years, an additional group of unexpected players have been recognized as key regulators of HSC specification: proinflammatory signals. Several excellent reviews regarding these novel HSC regulators have been published recently and can complement the current review [9–16]. Due to the novelty of this breakthrough, many questions remain concerning how proinflammatory signals operate to determine the HSC fate from the ventral aortic endothelium. In this review we seek to synthesize the inflammatory inputs that HSCs need for their emergence and bring to light the fundamental questions to be addressed to advance this rapidly progressing field.

The Signaling Basis of Classical Inflammation

Tissue disruption due to injury or pathogenic agents leads to the release of **proinflammatory cytokines** that result in **classical inflammation**. This process entails changes in gene expression and cellular function to eliminate the cause of the cellular injury and initiate tissue repair. It is surprising that the key pathways underlying the canonical responses to infection and inflammation are required to generate the founders of the adult hematopoietic system, since the emergence of HSCs from the aortic floor occurs in the aseptic embryo, whether *in utero* in mammals or in the chorion in teleosts. The proinflammatory mediators that regulate HSC development include **Toll-like receptors (TLRs)**, cytokines, and **eicosanoids**, each of which typically activates the immune system to fight infections. Proinflammatory mediators are generally studied under pathological conditions. In this regard, myeloid cells (i.e., macrophages and neutrophils) are armed with TLRs and **nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs)**, which, on recognition of danger- and pathogen-associated molecular patterns (DAMPs and PAMPs), induce the production of proinflammatory cytokines and eicosanoids [17–20]. TLRs promote the induction of gene expression and the intracellular accumulation of the major proinflammatory cytokines interleukin (IL)-1 β and IL-18 via the master inflammation/immune transcription factor nuclear factor kappa B (NF- κ B). Subsequently, recognition of PAMPs/DAMPs in the cytosolic compartment by NLRs promotes caspase-1-mediated proteolytic cleavage and release of proinflammatory cytokines and cytosolic phospholipase A2-mediated eicosanoid biosynthesis. Proinflammatory cytokines and eicosanoids then activate immune cells to eliminate the cause of infection and restore healthy tissue (Figure 1).

Adult HSCs Respond to Immunoregulators

Previously it was assumed that adult HSCs rarely divide and behave independently of extrinsic factors; however, it has become clear that HSCs respond dynamically to locally (niche/microenvironment) and distally (injury or infection) produced cytokines, including proinflammatory cytokines, chemokines, and PAMPs [10,21,22]. Illustrative of such a response is the ability of HSCs to skew normal hematopoiesis towards myelopoiesis, often at the expense of lymphopoiesis and erythropoiesis, in a process termed emergency or stress-induced hematopoiesis (for reviews see [23,24]). This compensatory response is helpful in boosting the basal production of myeloid cells due to the decrease in the number of myeloid cells as they are recruited to the site of infection. To ensure a proper response to inflammation, HSCs and hematopoietic stem and progenitor cells (HSPCs) must be able to indirectly (through proinflammatory cytokines or DAMPs) or directly (through PAMPs) sense the type of infection. While HSCs themselves are rarely infected by intracellular pathogens, they do express TLRs that on recognition of PAMPs can trigger cell cycle entry and differentiation to myeloid-committed progenitors [25,26]. An important step in this response may be the production and secretion of proinflammatory cytokines by the HSCs themselves, including tumor necrosis factor alpha (TNF- α), granulocyte/macrophage colony-stimulating factor (GM-CSF), and IL-6. The

Glossary

Classical inflammation: a complex biological process in which a tissue disruptor (pathogen or injury) is sensed, typically by immune cells, leading to the production of proinflammatory cytokines that activate the immune system to eliminate the cause of the disruption. In addition, tissue-resident cells and endothelial cells are activated to restore healthy tissue.

Eicosanoids: lipids that act in the proximity of the producer cell to regulate inflammation.

Embryonic stem cells (ESCs): cells obtained from an early-stage embryo (blastocyst) that are pluripotent and self-renew.

Graft-versus-host disease: a medical complication that often occurs following allogeneic transplantation in which donor lymphocytes react against host tissues.

Hematopoietic stem cell transplantation (HSCT): therapy utilized clinically to treat patients with blood cell disorders. HSCs are isolated from the patient (autologous transplantation) or from histologically compatible umbilical cord or bone marrow (allogeneic transplantation) and injected into the patient to regenerate the hematopoietic system.

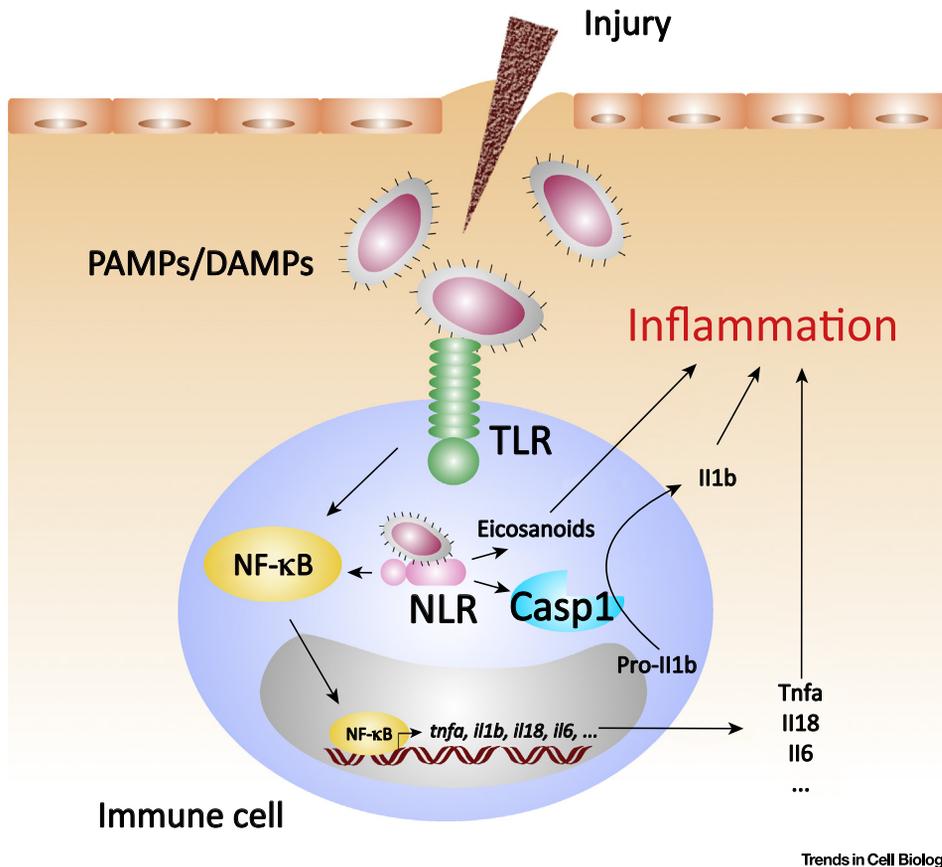
Hemogenic endothelium (HE): specialized arterial endothelial cells that give rise to HSCs.

Induced pluripotent stem cells (iPSCs): differentiated adult cells that have been genetically reprogrammed to adopt an embryonic stem cell-like state.

Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs): intracellular proteins that sense PAMPs or DAMPs to activate the immune response.

Proinflammatory cytokine: a type of cytokine (a small protein that produces changes in cell signaling) that promotes inflammation.

Toll-like receptors (TLRs): transmembrane proteins expressed by immune cells that recognize structurally conserved molecular patterns derived from pathogens (PAMPs) or damaged tissues (DAMPs) to elicit gene expression changes in the producer cell that activate the production of proinflammatory cytokines to fight infection.



Trends in Cell Biology

Figure 1. Cartoon Depicting the Key Steps in Classical Inflammation. Classical inflammation is a complex process that involves the recognition of harmful stimuli (pathogens, irritants, etc.) by immune cells, triggering the release of proinflammatory cytokines that will result in the clearance of infectious agents and reestablishment of healthy tissue. Abbreviations: Casp1, Caspase 1; DAMPs, danger-associated molecular patterns; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; IL-18, interleukin-18; NF- κ B, nuclear factor kappa B; NLR, nucleotide-binding oligomerization domain (NOD)-like receptor; PAMP, pathogen-associated molecular pattern; TLR, Toll-like receptor; TNF- α , tumor necrosis factor alpha.

proinflammatory cytokines produced and secreted by HSCs are dependent on NF- κ B function. These factors aid the maturation of myeloid and lymphoid cells and also stimulate an autoregulatory step to further expand myelopoiesis [21]. Interestingly, short-term HSCs and multipotent progenitors are more efficient in producing cytokines than mature immune cells in response to stimulation with TLR ligands [21], although the biological significance has not been addressed.

Interferons (IFNs) are a class of immune mediators known mainly for their critical roles in the activation of the immune system to fight viral infections. Type II IFN (IFN- γ or immune), but not type I IFN (IFN- α or non-immune), has also been shown to promote HSC proliferation in response to chronic infection [27]. Furthermore, HSCs from IFN- γ -deficient mice have a lower proliferative rate, indicating that baseline IFN- γ tone regulates HSC activity [27]. However, IFN- α has been found to exert opposing effects on HSC proliferation *in vivo* depending on the exposure time [28]. These findings implicate IFN- γ as a regulator of HSCs both during homeostasis and under conditions of infectious stress.

TNF- α is a pivotal proinflammatory cytokine whose role in the regulation of adult HSC activity has remained unclear. While one study showed that TNF- α restricted HSC activity in mice [29],

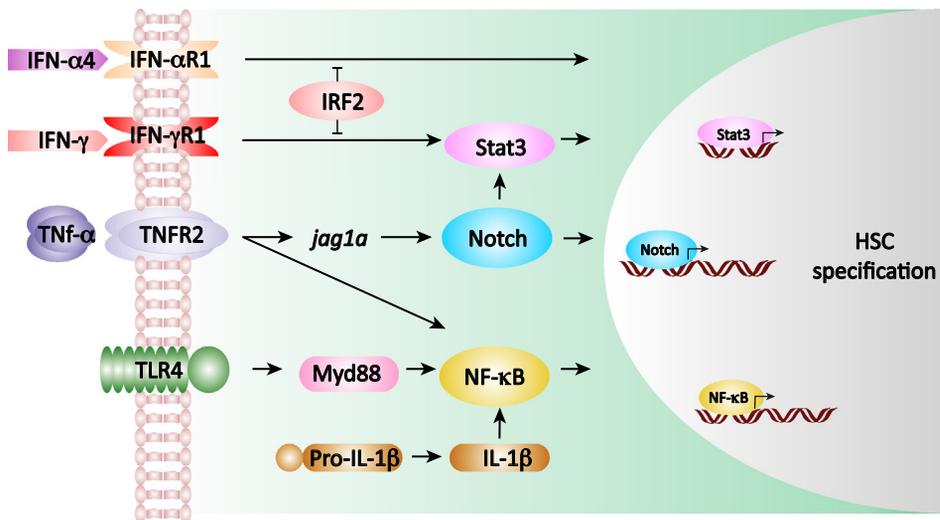
others have reported that genetic inactivation of TNF receptor (TNFR) 1 [30] or neutralization of TNF- α [21] impaired proliferative and self-renewal abilities. In addition, membrane-anchored TNF- α has been found to enhance the engraftment of purified HSCs in allogeneic and syngeneic recipients [31]. Together these findings highlight the importance of inflammatory mediators in the regulation of HSC function and homeostasis.

Inflammatory Cues in the Development of HSCs

Proinflammatory Cytokines as Key Regulators of HSC Development

Interestingly, the role of immunomodulators is not limited to adult HSC function. The first observations suggesting that proinflammatory pathways might be required to establish the hematopoietic system during embryogenesis in both vertebrates and invertebrates date from the late 1990s [32]. These studies linked the prototypical proinflammatory transcription factor NF- κ B with the formation of the hematopoietic system (for a review see [16]). However, it was not until 10 years later that additional studies started to specifically explore the effect of immunomodulators on HSC specification, emergence, and maintenance. IL-3, which is a cytokine that regulates the function, proliferation, and differentiation of immune cells, was found to promote the proliferation and survival of HSCs in the murine aorta–gonad–mesonephros (AGM) region (site of HSC specification) acting downstream of Runx1, an essential transcription factor in HSC specification [33]. In addition, evidence that another proinflammatory cytokine, IL-1, one of the hallmark regulators of inflammation, plays an active role in HSC development was reported [34]. In this study the authors showed that, at E11, murine IL-1 is highly expressed by HSCs while IL-1 receptors are detected in endothelium, mesenchymal cells, and, to some extent, HSCs themselves in the AGM region. The authors showed that the IL-1 pathway plays a critical role during HSC development, enhancing HSC expansion [34]. Around the same time, a second study utilized the zebrafish (*Danio rerio*) to screen for biological compounds able to enhance HSC production in the embryo and identified prostaglandin E2 (PGE2), a major regulator of inflammation, as a potent inducer of HSC emergence or expansion [35]. PGE2 was later shown to control Wnt autonomously in HSCs at the level of beta-catenin degradation through cAMP/PKA-mediated stabilizing phosphorylation events [36]. This discovery in the zebrafish has been translated to clinical settings, where 16,16-dimethyl-PGE2 (dmPGE2), a more stable derivative of PGE2, is currently being used in clinical trials in patients undergoing umbilical cord blood transplantation (UCBT) [37,38]. This is a good example of how the study of HSC formation in tractable vertebrate models such as zebrafish may benefit human health.

Collectively these studies suggested that immunomodulators may help expand HSCs during their development. However, the discovery that proinflammatory signals are required to establish the HSC fate from the HE was not made until recently, when it was shown that the proinflammatory cytokines TNF- α [39–41], IFN- γ [41,42], and IL-1 β [40,41], in addition to TLR4 signaling [40], are each a key determinant of HSC specification (Figure 2). TNF- α has been extensively studied in the context of inflammation and, to some extent, in adult hematopoiesis following immunological challenge. The ease of epistatic studies in the zebrafish allowed the determination that TNF- α acts through TNFR2 to specify HSCs from the HE [39]. Activation of TNFR2 was required for the expression of *jag1a* (Figure 2), a Notch ligand essential for HSC specification in the dorsal aorta. Expression of Jag1a, in turn, signals to the Notch1a receptor on adjacent HE to help establish the HSC fate. Thus, this work linked a proinflammatory cytokine with the Notch signaling pathway, a classical juxtacrine signaling system long known to regulate HSC emergence in vertebrates [43–45]. In addition, the proinflammatory transcription factor NF- κ B was active in nascent HSCs (Figure 2), being indispensable for their specification. Similar requirements for TNF- α and NF- κ B in HSC specification were found in both zebrafish and mouse embryos [40,41]. By sequencing of *runx1*⁺ HSCs obtained by fluorescence-activated cell sorting (FACS) in zebrafish, it was found that TNFR2, the NF- κ B



Trends in Cell Biology

Figure 2. Proinflammatory Signals Required for Hematopoietic Stem Cell (HSC) Specification. Toll-like receptor 4 (TLR4), tumor necrosis factor receptor 2 (TNFR2), and interleukin-1 β (IL-1 β) converge on nuclear factor kappa B (NF- κ B) activation, which acts upstream of Notch to specify HSCs. In addition, interferon gamma (IFN- γ), through IFN- γ receptor 1 (IFN- γ R1) and signal transducer and activator of transcription 3 (Stat3), and IFN- α 4, through its receptor IFN- α R1, function downstream of Notch in this process. Abbreviations: IRF2, IFN regulatory transcription factor 2; jag1a, jagged 1a; Myd88, myeloid differentiation primary response gene 88; TNF- α , tumor necrosis factor alpha.

member p65, and the sensor of bacteria-derived LPS, TLR4, are upregulated in HSCs [40]. Further exploration revealed that TLR4, together with IL-1 β and TNF- α , is required for HSC specification acting upstream of NF- κ B and Notch (Figure 2). TLR4 was found to be required in murine HSC specification, showing conservation across vertebrate phyla. Other proinflammatory players have therefore been added to the list of signals involved in HSC specification.

At the same time, it was demonstrated that HSCs, but not endothelial cells, rapidly respond to IFNs [41]. IFN- α 4 [41] and IFN- γ [41,42] are also needed for HSC specification across vertebrates through IFN α R1 and IFN γ R1, respectively. Unlike TNF- α and TLR4 signaling, IFN- γ acts downstream of Notch signaling and blood flow by activating Stat3 [41,42] (Figure 2). IFN- γ signaling acts autonomously in the HE [42]. The list of proinflammatory mediators that play roles during HSC specification has thus grown markedly over the past few years. Possible roles of many other proinflammatory cytokines in HSC formation and function remain unexplored. It is of great interest to the HSC field to refine the inflammatory requirements that HSCs need for their generation from the HE. Due to the novelty of inflammatory inputs here, many questions remain concerning how each of the known required inputs operates to generate HSCs from the ventral aortic endothelium. We hope that a more precise understanding of these signaling elements will inform *in vitro* approaches to ultimately create patient-specific HSCs.

The Role of Immune Cells in HSC Emergence

An important question arising from the above discussion is: what are the cellular sources of proinflammatory cytokines? Based on their functions in adult inflammation, immune cells would be logical sources. However, since HSC emergence occurs before the immune system is fully formed, the only cells present during these early developmental stages are macrophages and neutrophils that have arisen from previous waves of transient developmental hematopoiesis [46]. Whereas murine macrophages have a demonstrated impact on adult HSCs by regulating the HSC bone marrow niche [47], their retention/mobilization [48,49] and also their function [50,51] – the role of ‘primitive’ macrophages in embryonic HSC development – is only starting to

be deciphered. One study suggests that macrophages directly interact with emerging HSCs and produce metalloproteases to break down the extracellular matrix surrounding emerging HSCs to create 'space' for migration and expansion [52]. Chemical and genetic depletion of macrophages in the embryo led to an increase of HSCs along the dorsal aorta, possibly due to their inability to leave their site of emergence and migrate throughout the underlying mesenchyme. While macrophages have been extensively studied and assigned a variety of functions, little is known about the role of neutrophils during development [53]. Interestingly, 'primitive' neutrophils appear to be essential for HSC specification, since depletion of macrophages/neutrophils leads to a decrease in HSC number whereas increasing neutrophil numbers results in an increase in HSCs [39,40]. In addition, a recent study suggests that neutrophils and endothelial cells are major sources of metalloproteases in the embryo, which may assist in EHT events [54]. Another, less obvious source of proinflammatory cytokines in the embryo is the HSCs themselves [40] and their endothelial niches [39]. The relative contributions of these potential sources to HSC emergence/maintenance remain to be explored.

Concluding Remarks

Proinflammatory signals have been classically believed to downregulate stem cell activity; however, this concept has been challenged in recent years due to accumulating evidence that proinflammatory signals positively regulate SCs in settings of tissue repair and regeneration [55]. HSCs are born in the developing embryo. The complex processes of tissue formation and regeneration after tissue damage frequently involve the same molecular signaling pathways [56,57]. It thus may be unsurprising that proinflammatory signals regulate HSC formation. In the HSC field, it has been recently shown that proinflammatory signaling is indispensable for the normal emergence of HSCs. To date, TNF- α , IL-1 β , IFNs, PGE2, TLR4, and NF- κ B have been identified as regulators of HSC specification, emergence, and maintenance. These are, however, only a subset of the known proinflammatory cytokines. Despite the increase in our knowledge of how proinflammatory cytokines regulate HSC formation, several fundamental questions remain (see Outstanding Questions). Hence, it is worthwhile to evaluate other proinflammatory players, including NLRs and the inflammasome and additional TLRs and interleukins, as well as anti-inflammatory cytokines. Hints that other proinflammatory factors might also be important for HSC biology come from studies showing that TLR2 and TLR9, among others, are expressed in adult HSCs and CD34⁺ cord blood cells, respectively [58,59]. Furthermore, activation of NLRP1a by periods of hematopoietic stress prolongs cytopenia, bone marrow hypoplasia, and immunosuppression [60]. However, the potential contribution of these TLRs and NLRs during HSC development has not yet been addressed. Migration or homing is an important feature of HSCs as they reside in different hematopoietic tissues after their emergence. In general, chemokines play an important role in SC recruitment into their niche. Specifically for HSCs, it was shown that IL-8, also termed CXCL8, induces the mobilization of adult HSCs [61] and mediates embryonic HSC expansion across vertebrate species [62,63]. Regarding these results, it would be of interest to also evaluate the contribution of other chemokines such as CCL2, CCL3, and CCL5 in the context of HSC emergence.

Importantly, the contribution of the immune system to HSC emergence is not limited to the production of inflammatory mediators. Rather, a variety of additional roles for immune cells have recently become apparent. Before HSCs are produced in the vertebrate embryo, several transient waves of hematopoiesis give rise to erythrocytes, macrophages, and neutrophils [64–66]. It has been classically postulated that these primitive myeloid cells may help the embryo to fight infections. However, the developing embryo is largely protected against pathogens in the uterus in mammals or inside the chorion in fish. Why, then, has nature equipped the early developing embryo with these primitive immune cells? One possible explanation may be that these early immune cells play roles in developmental processes, as recent research is starting to show. A second interesting question that arises is how primitive

Outstanding Questions

What is the role of HSC-expressed proinflammatory cytokines/receptors? Might they reinforce positive signaling loops within HSCs to amplify the proinflammatory signals received? Might they play an autocrine/paracrine role in HSC development and differentiation?

Which genes are regulated by proinflammatory cytokines that help specify HSCs?

Which are the signals that elicit developmental inflammation in the embryo to specify HSCs?

Will the addition of proinflammatory cytokines ultimately aid protocols to obtain long-term, multilineage HSCs?

macrophages and neutrophils are activated to produce and release these proinflammatory cytokines during development. There are many potential triggers during normal development that may stimulate production. For example, due to the rapid growth of tissue and organs, local pockets of hypoxia are created [67–69]; in addition, apoptosis [70], senescence [71–73], and/or autophagy might lead to the activation of immune cells during embryogenesis.

Since it has become clear that proinflammatory mediators participate in HSC specification, emergence, and maintenance *in vivo*, it will be important to evaluate each one for potential contributions to HSC instructions *in vitro*. A recent study attempted to evaluate whether TNF- α , IFN- γ , or IL-1 β had an impact on the number of hemogenic endothelial or hematopoietic precursors generated from human pluripotent stem cells [74]. Although no differences in numbers of hemogenic endothelial precursors or hematopoietic cells were found, these studies are difficult to fully interpret since the generation of functional HSCs from iPSCs is not currently possible. As the proinflammatory factors implicated in HSC emergence appear to be HSC specific, this hurdle is likely to need to be overcome before the *in vitro* effects on HSC production can be accurately determined.

The notion that proinflammatory signals are important in shaping the hematopoietic system has been relatively slow to develop, which is likely to be due, at least in part, to the fact that many knockout mice in which proinflammatory signals are ablated lack obvious hematological defects. This may be due to genetic compensation or redundancy between proinflammatory pathways. In support of the latter postulate, knockdown of both TNF- α and IFN- γ led to substantial decreases in HSC numbers compared with either single knockdown [41]. An interesting approach to avoid redundancy or compensatory mechanisms is the use of lower-vertebrate or invertebrate animal models. For example, in *Drosophila melanogaster* the more than ten TLRs described in vertebrates and five NF- κ B subunits are reduced to a single Toll–Cactus–Dorsal signaling axis, which allowed the early discovery in the 1990s of its crucial role in developmental hematopoiesis [75]. By contrast, to resolve the role of NF- κ B in murine hematopoiesis, double knockout mice for both NF- κ B subunits had to be generated (for a review see [16]). Thus, the simplification of these pathways using less complex animals may provide valuable hints to understanding the roles of inflammatory signaling in SC development.

In line with the discussion presented here on the unconventional role of the immune system during development are the recent findings that variations on the classical inflammatory response exist in other scenarios. These include ‘meta-inflammation’ [76], the inflammatory response orchestrated by nutritional and metabolic cues. In addition, ‘inflammaging’ [77], has been presented as age-related inflammation resulting from systemic physiological processes involving most of the cells and organs of the body. These types of inflammation also occur in the

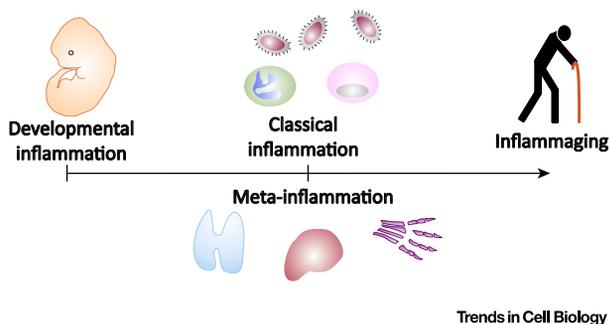


Figure 3. The Four Types of Inflammation. Classical inflammation results in activation of the immune system and the release of proinflammatory cytokines as a result of pathogenic or injury challenge. By contrast, in developmental inflammation, meta-inflammation, and inflammaging, the increases in proinflammatory signatures are physiological in response to embryo development, metabolic changes, and age, respectively.

Trends in Cell Biology

absence of infection. Perhaps it is now time to recognize ‘developmental inflammation’ as a novel variation that helps produce and shape key organs and cells during normal embryonic development, including HSC formation (Figure 3). Ultimately, the signaling elements used in classical inflammatory responses may represent evolutionary adaptations of pathways initially utilized for the control of developmental events.

Acknowledgments

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