Inflammaging of Hematopoietic Stem Cells

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Hematopoietic stem cells (HSCs) sustain the lifelong production of all blood cell lineages. The functioning of aged HSCs is impaired, including a declined repopulation capacity and myeloid and platelet-restricted differentiation. Both cell-intrinsic and microenvironmental extrinsic factors contribute to HSC aging. Recent studies highlight the emerging role of inflammation in contributing to HSC aging.

Keywords: hematopoietic stem cells ; aging ; inflammation

1. Introduction

With age, a chronic, systemic and low grade inflammatory process is referred to as inflammaging, which is associated with immunosenescence and age-related diseases [1][2]. There is evidence indicating that inflammaging occurs in hematopoiesis under chronic inflammatory stress. Interestingly, inflammation-associated stress hematopoiesis is very similar as age-associated hematopoiesis, discussed above. For example, chronic inflammatory signals cause the expansion of HSC and GMP and a reduction of CLP and RBC [3][4]. Similar phenotypes emerge during experimental spondyloarthritis in which mice developed non-resolving inflammation [5]. In addition, consecutive injections of LPS dramatically suppressed erythropoiesis [6]. Most importantly, increasing evidence demonstrates that multiple pro-inflammatory cytokines, including IL-1β [7][8], TNF-α [9], IL-6 [8] and TGFβ1 [10], are present at increased levels in aged BM (Table 1). The inhibition of both IL-1β and TNF-α in aged mice attenuated myelopoiesis [11]. This indicates that aged HSCs are exposed to a niche containing more pro-inflammatory cytokines, which likely contributes to the age-associated HSC dysfunctions. This also suggests that the inhibition of inflammatory responses may rejuvenate aged HSC.

Table 1. The role of pro-inflammatory cytokines in hematopoiesis and their altered expression during aging.

Stimuli	Source	Effects on HSC	Change with Age	Reference
IFN-α	Plasmacytoid dendritic cells, macrophages	Transient proliferationImpaired repopulation potentialExhaustion		[12][13][14]
IFN-γ	T cells, Th1 cells, macrophages	ProliferationImpaired repopulation potentialExhaustion		[15][16]
IL1-β	Monocytes, macrophages, ECs,	Myeloid differentiationImpaired repopulation potential	Up	[3][4][17][18][19]
TNF-α	Macrophages, T cells, NK cells	Myeloid differentiation	Up	[20][18]
IL-6	MSCs, macrophages	Myeloid differentiation	Up	[4][21]
GM-CSF	MSCs, ECs, macrophages, T cells	Myeloid differentiation		[22]
G-CSF	MSCs, ECs	Myeloid differentiation		[23][24]
TGFβ1	MSCs, Mks	QuiescenceExpansion of myeloid-biased HSC	Up	[2][25]
LPS	Gram-negative bacterial infections	ProliferationImpaired repopulation potential		[26][27]

ECs: endothelial cells, MSCs: mesenchymal stromal cells, Mks: megakaryocytes.

2. HSCs Are Transiently Activated under Chronic Inflammation

HSCs proliferate in response to both interferons (IFNs) type-I (IFN-α/β) [28][29][30][31] and type-II (IFN-γ) [32], interleukin (IL)-1 [3], tumor necrosis factor (TNF)-α [33], G-CSF [34] and TLR ligands [35] (Table 2). IFN-α, for example, induces cell

cycle entry by suppressing the expression of cyclin-dependent kinase inhibitors (CDKIs), which results in decreased expression of *Cdkn1b* (*p27*) and *Cdkn1c* (*p57*) [30][31]. After chronic exposure of HSC to LPS, IL1-β or IFN-γ enhanced proliferation is induced [3][35][36]. Moreover, IFN-α and IL1-β inhibit HSC proliferation in vitro whereas IFN-γ, TNF-α and TLR ligands directly accelerate HSC proliferation in vitro [3][33][30][37][35], indicating that distinct signals promote HSC proliferation via different mechanisms. For instance, it has been demonstrated that a transcriptional suppressor of type I IFN signaling, interferon regulatory factor-2 (IRF2), negatively regulates HSC proliferation and $Irf2^{-/-}$ HSCs show enhanced cell cycling status [31].

Increased HSC proliferation under inflammation is rapid but transient [33][30][38]. For instance, HSCs quickly return to a quiescent state, and p27 and p57 return to steady-state levels during in vivo chronic exposure to IFN-α [30]. Therefore, HSCs maintain a largely quiescent state during chronic inflammatory stress induced by polyinosinic-polycytidylic acid (poly I:C) [30], mimicking type I IFN-mediated response, IL1-β and chronic inflammatory arthritis, regardless of cell cycle activation at early phase of treatment [39][33][30][38]. This quiescent state under chronic inflammation is due to the repression of cell cycle and protein synthesis genes, which are mediated by activation of the transcription factor PU.1 and direct PU.1 binding at repressed target genes. Consistently, PU.1-deficient HSCs displayed overexpressed cell cycle and protein synthesis genes [40]. Aged HSCs display cell cycle arrest [41][42], which is associated with replicative stress [41]. Further studies are needed to investigate to what extent the dormant status of aged HSCs is caused by chronic exposure to inflammation.

3. Chronic Inflammation Triggers Myeloid-Biased Differentiation and Impaired Self-Renewal

Inflammatory signals activate HSC and promote myelopoiesis [33][5][43][44][45][46]. This response is beneficial in combatting infection, but chronic exposure to inflammatory insults impairs HSC self-renewal and causes stem cell loss. Most inflammatory stimuli have been reported to affect HSC multi-lineage differentiation and long-term repopulation potential (**Table 2**). HSCs grown in liquid culture with IL-1β produced more mature myeloid cells [3]. Furthermore, mice that were chronically exposed to IL-1β displayed increased myeloid cells at the expense of lymphoid cells. HSCs isolated from these mice displayed myeloid-biased differentiation potential and significant reduced self-renewal [3]. Of note, the impairment of HSC recovered after treatment, which is probably due to the reestablished quiescence. TNF-α also promotes myeloid regeneration in vitro [33][47]. Although no major changes in lineage distributions were observed from TNF-α-treated HSCs, these HSCs had severely compromised reconstitution abilities, which, similar to effects of IL-1β, recovered upon extra resting periods [3][33]. This demonstrates a transient impairment of the engraftment potential of IL-1β and TNF-a-treated HSCs [3][33]. Consistently, acute lipopolysaccharide (LPS) also induced transient changes in hematopoiesis, affecting epigenetic modifications and HSC gene expression [48]. Mice transplanted with LPS pre-stimulated HSCs displayed high survival against secondary bacterial infection [48]. However, chronic LPS treatment attenuated HSCs' self-renewal and competitive repopulation activity [35]. Thus, HSCs respond differently to acute and chronic inflammation, and only chronic and continuous inflammation mimics the aging-associated functional declines.

4. Inflammation-Associated Signals Are Activated in Aged HSCs

To date, we have limited knowledge of the mechanisms by which inflammatory signals regulate HSC function. Under chronic LPS exposure, the functions of HSCs were impaired in a TLR4-TRIF-ROS-p38-pathway dependent manner [35]. C/EBPβ is required for LPS-induced memory, which improves myeloid differentiation and the resistance to secondary infection [48]. The loss of C/EBPβ attenuates an IL-1β-driven myeloid gene program and expands hematopoietic stem and progenitor cells (HSPCs) [46]. It also has been shown that the induction of myeloid differentiation by IL-1β and TNF-α is likely due to the activation of PU.1 [3][40][47] and mice lacking the PU.1 upstream regulatory severely attenuated myeloid differentiation. The overexpression of PU.1 has been shown to accelerate the myeloid output of HSCs in vitro [3]. In addition, the TNF-α-dependent activation of PU.1 is directly regulated via NF-κB-dependent signaling [33][47]. Actually, the transient impairment of HSCs induced by TNF-α correlates with both cell cycle activation and the status of the NF-κB pathway [33], suggesting that this pathway is of vital importance for inflammatory hematopoiesis. Interestingly, NF-κB was shown to become activated in aged HSCs, documented by elevated phosphorylation and translocation in the nucleus [49][9][50]. This suggests that an active inflammatory response exists in aged HSCs at steady state and raises the possibility that NF-κB signaling pathway is a potential target to achieve rejuvenation of aged HSC.

5. Aged BM Niche Is Inflamed

Considering the fact that pro-inflammatory cytokines are elevated in aged BM, the aged niche is also an inflamed niche. Inflammation can remodel the BM niche as niche cells themselves express various inflammation-associated receptors and

thus contribute to HSC aging indirectly.

Exposure to LPS or poly I:C has shown to trigger bone marrow angiogenesis with an increased number of sinusoids, an increase in integrin αVβ3 expression and activation on ECs and vascular leakiness [51][17]. BM ECs, expressing high level of *Tlr4* and myeloid primary response gene 88 (*Myd88*), are the primary source of granulocyte colony-stimulating factor (G-CSF), the key granulopoietic cytokine, after LPS challenge or *Escherichia coli* infection. Therefore, ECs are essential cells for emergency granulopoiesis under systemic bacterial infection [20]. Consistent with this, young HSPCs cocultured on aged ECs acquired a myeloid bias with a decrease in B and T cell frequencies, and an in vivo infusion of aged endothelium into young recipients impaired HSC self-renewal and induced myeloid bias [52].

Aged BM stroma cells show increased expression of inflammatory chemokines (*Cxcl2* and *Cxcl5*) and several members of the complement cascade (*Cfd*, *Cfb*, *C4b*, and *C3*). Most importantly, *Il1b* and *Il6* expression levels are increased [53]. Likewise, aged BM macrophages also showed upregulation of *Il1b* [7]. These data are consistent with the accumulation of both cytokines in the aged BM [7][8], which supports the positive feedback that BM niche cells respond to inflammation to secrete more inflammatory cytokines, which in return enhance pro-inflammatory responses of niche cells (**Figure 1**). The expression of multiple pathogen sensors, *Tlr4* for example, and various effector molecules, including *Erk1*, *Elk1* and *Tbk1*, were increased in old plasma cells, indicating that old plasma cells were primed for TLR mediated inflammatory response [11]. Functionally, aged plasma cells stimulated myelopoiesis, and inhibited lymphopoiesis, when cultured with HSCs ex vivo and in vivo plasma cell depletion, reversed the age-associated enhancement of myelopoiesis [11].

6. Heterogeneous Response of HSCs to Inflammation

Considering the fact that pro-inflammatory cytokines are elevated in aged BM. We described earlier how HSCs can directly respond to inflammatory stimuli as they express multiple receptors known to interact with inflammatory ligands. This raises the notion that heterogeneous responses of HSCs to inflammation may result if those receptors are heterogeneously expressed on HSCs. As discussed above, HSCs are phenotypically and functionally heterogeneous. Thus, there may be subsets of HSCs that show different responses to inflammatory insults. Single cell RNA sequencing has identified HSC subsets with distinct transcriptional responses to inflammatory signals [54]. For example, type I IFN, TNF, and IL-1β all expanded CD41^{high} and P-selectin^{+} (Selp^{+}) HSCs. The high expression of CD41 coincides with stem-like megakaryocyte-committed progenitors within the HSC pool, and the expansion of this pool is associated with activated megakaryopoiesis [28][3]. Upon chronic LPS treatment, CD86^{+} HSCs, primed for lymphoid-biased differentiation, were reduced [4]. IL27Ra marks a population with impaired self-renewal and myeloid-skewing. This subset expanded when exposed to TNF-α. Of note, RNA-sequencing revealed that IL27Ra^{+} HSCs displayed inflammatory signatures in comparison with IL27Ra^{-} HSCs, indicating that there are HSC subsets that are primed for potential inflammatory stress during homeostasis [9].

IL-6R and TLR4 were shown to be more abundantly expressed by old myeloid-biased HSCs, indicating that aged HSCs sense inflammation signals differently compared to young HSCs. Indeed, aged HSCs have differential responses to inflammatory challenges compared to young HSCs [54]. Aged HSCs showed more skewed myeloid differentiation in vivo after 2 h culture with LPS, while young HSCs still maintained a balanced output [54]. Furthermore, the frequency of HSC subsets with heterogeneous transcriptional profiles to inflammatory signals also alters with age [54]. Specifically, inflammation-related genes were more enriched in the aged compared to the young IL27Ra^{+} HSCs, suggesting that IL27Ra^{+} HSCs are inflamed and the inflamed situation accumulates with age [9]. Collectively, this suggests that responses of HSC to inflammation changes with age as well. The changes in inflammatory responses with aging are likely due to the changes of HSC composition, where HSC subpopulations primed for inflammatory insults expand. Indeed, CD41 [55], Selp [18][49][56] and IL27Ra [9] are up-regulated with aging in HSCs (**Table 1**), which is largely due to the expansion of specific populations.

Most importantly, HSC subsets with inflammatory signatures displayed dysfunctions that are very similar to those induced by age. Collectively, a large part of age-associated HSC changes is likely caused by a dominance of inflamed HSCs that are further expanded by elevated inflammatory signals in the aged BM. In other words, inflamed HSCs may display age-associated functional decline and those inflamed HSCs are functionally “older”. In the aged BM, we suggest that less inflamed HSC subsets exist, which are functionally “young-like” and have a high stem cell potential.

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