Inflamm-aging of hematopoietic stem cells

Zhiyang Chen, Zhenyu Ju*

Key Laboratory of Regenerative Medicine of Ministry of Education, Guangzhou Regenerative Medicine and Health Guangdong Laboratory, Institute of Aging and Regenerative Medicine, Jinan University, Guangzhou, China

Abstract

Hematopoietic stem cells (HSCs) are responsible for generating all blood cells throughout life. Apart from the role of HSCs in maintaining the homeostasis of blood cell production process, they must respond quickly to hematopoietic challenges, such as infection or blood loss. HSCs can be directly/indirectly activated and engage in blood formation for the acute needs in response to inflammation. Recent findings highlight the emerging role of inflammation signaling on HSC fate decision and shaping the hematopoietic system during aging. Here, we summarize recent studies identifying the changes in inflammation and their role in modulation of HSC function and discuss the interaction between inflammation and HSC biology in the contexts of aging and hematological malignancy.

Keywords: Hematopoietic stem cell, Inflammation, Aging, Hematologic malignancy

1. INTRODUCTION

Organism aging is characterized by increases in inflammation and decrease in stem cell function. Stem cells contribute to tissue maintenance over the lifetime. An age-dependent decline in stem cell function occurs in various tissues, especially those with a high cellular turnover rate and this decline contributes to impairments in tissue homeostasis during aging.[1,2] In the blood system, since mature blood cells are short-lived, hematopoietic stem cells (HSCs) are required and can continuously provide all hematopoietic and immune cells through a highly organized process to maintain life-long hematopoiesis.[3] In addition to the essential role of HSCs in the steady-state and the maintenance of hematopoiesis under the stress conditions, HSCs could sense and respond to the infectious in many different ways. First, the HSCs itself could be infected by the pathogens which leads to a direct effects on HSCs organelles; second, the pathogenic organisms may signal directly to HSCs by releasing pathogen-associated molecular patterns (PAMPs) which active pattern recognition receptors on HSCs; third, the infection may lead to an alteration in the HSC microenvironment, such as an increase in the cytokines.[4–7]

Chronic increases in inflammation have been identified as a hallmark of aging and are associated with accelerated disease development.[8,9] Extensive attention has been paid to understand the relationship between inflammation and aging and their effects on HSC function. As early stages of cancer development are often associated with a substantial increase in inflammation,[10] understanding the intersection of these two processes could also be relevant for perceiving the mechanism of disease development in blood system during aging. In this review, we detail the impact of inflammation on HSC function in the contexts of aging and disease development.

2. INFLAMMATION REGULATES HSC FATE

During hematopoietic stress, such as inflammation, short-lived immune cells are activated and consumed.[11,12] Given its fundamental role in generating mature blood cells, HSCs activation ensures efficient replenishment of blood and immune cells upon inflammation.[4] A growing body of studies has detailed the impact of the inflammation signals, most of all are cytokines, on HSC fate decision.[7,13–16] Of note, the same cytokines can act in different ways under different conditions. For example, both IFN-a and IFN-g has dual functions of promoting or inhibiting HSC, depends on the acute and chronic infection conditions or the concentrations of cytokines. In response to inflammation, HSCs are quickly called into the cell cycle and differentiate into mature cells, which is essential for emergency hematopoiesis. However, the inflammation-induced cycling of HSCs leads to stem cell exhaustion.[5–7] Interestingly, a small proportion of HSCs return to quiescent state in order to prevent the stem cell pool exhaustion with an unknown mechanism.[17] HSCs reside in a dormant state in the microenvironment, which is called niche.[18] Upon inflammation stimulation, HSCs are mobilized from their niche, suggesting that inflammation disturb HSC-niche interaction.[19] Inflammation signals also have been shown to disrupt the balance between HSC self-renewal and differentiation. Chronic inflammation leads to HSC lose self-renewal. A study conducted in the mouse model clearly shows that repeated exposures to inflammatory stimuli such as LPS, negatively affected HSC function.[5] Furthermore, inflammation drives myeloid fate decisions in HSCs and reduces lymphopoiesis.[4,6,15]

* *Address correspondence: Zhenyu Ju, Key Laboratory of Regenerative Medicine of Ministry of Education, Guangzhou Regenerative Medicine and Health Guangdong Laboratory, Institute of Aging and Regenerative Medicine, Jinan University, Guangzhou, China. E-mail address: zhenyuju@163.com (Z. Ju).*

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Earlier studies on the effects of inflammation on the hematopoietic system were focused on mature immune cells, the first responders of inflammation. The response by HSCs and progenitors was initially thought to be compensatory to ensure sufficient production of mature immune cells consumed during an inflammation. New evidences, however, suggest that HSCs respond to inflammation stimuli directly.[5,6] HSCs could immediately respond to inflammation via cytokine receptors, Toll-like receptors (TLRs), and activate the NF-κB pathway, instead of sensing a depletion of downstream cells.[6] In response to inflammation, HSPCs produce copious amounts of cytokines, especially IL-6, which rapidly induces HSCs to differentiate into myeloid cells.[6] These studies highlight the importance of HSCs and progenitors behave as the first responders to inflammation have changed our fundamental understanding of HSC biology.

3. INFLAMMATION IN HSC AGING

HSC aging includes several key phenotypes: the number of phenotypically defined HSCs in bone marrow increases 2- to 10-fold during aging, the regenerative capacity of HSCs declines with age and do not regenerate the hematopoietic system damaged by stress, injury, or attrition as efficiently as young HSCs.[20–22] In addition, aged HSCs exhibit a skewed differentiation potential generating decreased numbers of lymphoid cells but increased numbers of myeloid cells, which is associated with impaired immune function and with an increased incidence of myeloid leukemia.[23,24] Inflammation induces phenotypically defined HSC number and loss of self-renewal coupled with impaired and myeloid-skewed differentiation, thus resembling some of the most prominent phenotypes of the aging hematopoietic system. It would be crucial to understand how aged HSCs response upon inflammatory stress. It has been shown that aged HSCs exhibit enhanced mobilization from bone marrow to blood in response to stimulation, such as treatment with chemotherapy or cytokines.[25] Moreover, HSCs from aged mice respond differently to inflammation challenge as compared with HSCs from young mice, those aged HSCs show a more myeloid-biased differentiation and a stronger reduction in losing self-renewal capacity.[26,27] The effect of inflammation on HSC self-renewal and differentiation may execute as a driving force of HSC aging.

4. INFLAMMATION IN HEMATOLOGICAL MALIGNANCY

Aging is associated with a chronic inflammatory phenotype characterized by increased secretion of an abundance of inflammatory proteins, termed the senescence-associated secretory phenotype (SASP).[28] Many recent researches have shown that cytokines, such as TNF, IFNs, IL-6, and IL-1, play a supporting role in several hematological diseases development, including myeloproliferative neoplasms, myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML).[29–33] Moreover, inflammation also contributes to the depletion of healthy HSC clones and induces HSC transformation into a preleukemic state.[27,34,35] Studies of the association between inflammatory cytokine signaling and HSC function may contribute to advances in the treatment for hematological malignancies. Since pro-inflammatory cytokines, such as TNF, or IFNs, can drive HSC differentiation, these cytokines could be applied therapeutically to accelerate the exhaustion of cancer stem cells in the hematological malignacies.[36,37] On the other hand, the potentially beneficial role of such cytokines in cancer treatment might come at the cost of accelerated emergence of cytokine resistant mutations in HSC compartments. These findings suggest a crucial role for SASP-associated cytokines in hematological disease progression and support a model that inflammation may function as a driver of hematological malignancy.

5. CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Since many hematopoietic malignancies are outcomes of deregulation of the HSC homeostasis during aging, a better understanding of how aged HSC homeostasis is maintained under inflammation stress is critical for clinical translation and practice. The knowledge of the inflammation contribution to HSC aging and disease development in the blood system is still limited, many open questions remain to be solved in the future.

A complex network of cell-intrinsic and extrinsic factors regulates HSC homeostasis during aging.[38] Altered intercellular communication is one of the hallmarks of aging, and a remarkable aging-associated alteration in intercellular communication is inflammation.[39] Undoubtedly, the knowledge of how intrinsic and extrinsic inflammation factors contribute to HSC aging and hematological disease development will help in understanding the aging process itself and might provide novel therapeutic means for the clinical treatment in the blood system.

Recently, it has been shown that macrophages maintain inflammatory memory, promoting an enhanced response to the following inflammatory insults.[40] This exacerbated response is a consequence of changes in the chromatin dynamics by which the enhancers regulating inflammatory response genes remain active. It remains to be studied whether a similar mechanism also exists at the HSC level. It will be of future interest to delineate the contribution of inflammatory memory and whether this may be involved in driving aging-associated phenotypes of the hematopoietic system.

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