Inflamm-aging of hematopoietic stem cells

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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.1–7 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.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 inflammation 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.17–19 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. 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
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. In response to inflammation, HSCs produce copious amounts of cytokines, especially IL-6, which rapidly induces HSCs to differentiate into myeloid cells. 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. 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. 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. 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. 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). 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). Moreover, inflammation also contributes to the depletion of healthy HSC clones and induces HSC transformation into a preleukemic state. 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 malignancies. 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. Altered intercellular communication is one of the hallmarks of aging, and a remarkable aging-associated alteration in intercellular communication is inflammation. 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. 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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REFERENCES

[1] Sharpless NE, DePinho RA. How stem cells age and why this makes us grow old. Nat Rev Mol Cell Biol 2007;8:703–713. doi: 10.1038/nrm2241.
[2] Rando TA. Stem cells, ageing and the quest for immortality. Nature 2006;441:1080–1086. doi: 10.1038/nature04958.
[3] Seita J, Weissman IL. Hematopoietic stem cell self-renewal versus differentiation. Wiley Interdiscip Rev Syst Biol Med 2010;2:640–653. doi: 10.1002/wsbm.86.
[4] King KY, Goodell MA. Inflammatory modulation of HSCs: viewing the HSC as a foundation for the immune response. Nat Rev Immunol 2011;11:685–692. doi: 10.1038/nri3062.
[5] Takizawa H, Fritsch K, K watering TK, et al. Pathogen-induced TLR4-TRIF innate immune signaling in hematopoietic stem cells promotes proliferation but reduces competitive fitness. Cell Stem Cell 2017;21:225–240.e5. doi: 10.1016/j.stem.2017.06.013.
[6] Zhao J, Lo C, O’Connell RM, et al. Conversion of danger signals into cytokine signals by hematopoietic stem and progenitor cells for regulation of stress-induced hematopoiesis. Cell Stem Cell 2014;14:445–459. doi: 10.1016/j.stem.2014.01.007.

[7] Eschen MA, Offner S, Blanco-Bose WE, et al. IFNalpha activates dormant hematopoietic stem cells in vivo. Nature 2009;458:904–908. doi: 10.1038/nature07815.

[8] Fagiolati UO, Cossarizza A, Scala E, et al. Increased cytokine production in mononuclear cells of healthy elderly people. Eur J Immunol 1993;23:2375–2378.

[9] Bruininga H, Pedersen BK. Age-related inflammatory cytokines and disease. Immunol Allergy Clin North Am 2003;23:15–39.

[10] Dolcet XD, Llobet D, Pallares J, Mattias-Guix X. NF-kB in development and progression of human cancer. Virchows Arch 2005;446:473–482.

[11] Medzhitov R. Origin and physiological roles of inflammation. Nature 2008;454:428–435. doi: 10.1038/nature07201.

[12] Manz MG, Boettcher S. Emergency granulopoiesis. Nat Rev Immunol 2014;14:302–314. doi: 10.1038/nri3660.

[13] Baldridge MT, King KY, Boles NC, Weksberg DC, Goodell MA. Quiescent hematopoietic stem cells are activated by IFN-g in response to chronic infection. Nature 2010;465:793–797.

[14] Matatall KA, Shen CC, Challen GA, King KY. Type II interferon promotes differentiation of myeloid-biased hematopoietic stem cells. Stem Cells 2014;32:3023–3030. doi: 10.1002/stem.1799.

[15] Pietras EM, Mirantes-Barbeito C, Fong S, et al. Chronic interleukin-1 exposure drives hematopoietic stem cells towards precocious myeloid differentiation at the expense of self-renewal. Nat Cell Biol 2016;18:607–618. doi: 10.1038/nclb3346.

[16] Sato T, Onai N, Yoshizawa H, Arai F, Suda T, Ohzeki T. Interferon regulatory factor-2 protects quiescent hematopoietic stem cells from type I interferon-dependent exhaustion. Nat Med 2009;15:696–700. doi: 10.1038/nm.1973.

[17] Pietras EM, Lakshminarasimhan R, Technier JM, et al. Re-entry into quiescence protects hematopoietic stem cells from the killing effect of chronic exposure to type I interferons. J Exp Med 2014;211:245–262. doi: 10.1084/jem.20131043.

[18] Pinto S, Frenette PS. Haematopoietic stem cell activity and interactions with the niche. Nat Rev Mol Cell Biol 2019;20(5):303–320.

[19] Kunisaki Y, Bruns I, Scheiermann C, et al. Arteriolar niches maintain hematopoietic stem cell quiescence. Nature 2013;502 (7473):637–643.

[20] Sahin E, Depinho RA. Linking functional decline of telomeres, mitochondria and stem cells during ageing. Nature 2010;464:520–528. doi: 10.1038/nature08982.

[21] Sperka T, Wang J, Rudolph KL. DNA damage checkpoints in stem cells, ageing and cancer. Nat Rev Mol Cell Biol 2012;13:579–590. doi: 10.1038/nrm3420.

[22] Pazhanisamy SK. Stem cells, DNA damage, ageing and cancer. Hematol Oncol Stem Cell Ther 2009;2:375–384.

[23] Geiger H, de Haan G, Florian MC. The ageing haematopoietic stem cell compartment. Nat Rev Immunol 2013;13:376–389. doi: 10.1038/nri3433.

[24] Verovskyay EV, Dellarusso PY, Passague E. Losing sense of self and surroundings: hematopoietic stem cell aging and leukemic transformation. Trends Mol Med 2019;17: pii: S1471-4914(19)30095-4.

[25] Liang Y, Van Zant G, Szilvasy SJ. Effects of aging on the homing and engraftment of murine hematopoietic stem and progenitor cells. Blood 2005;106:1479–1487. doi: 10.1182/blood-2004-11-4282.

[26] Mann M, Mehta A, de Boer CG, et al. Heterogeneous responses of hematopoietic stem cells to inflammatory stimuli are altered with age. Cell Rep 2018;25(11):2992–3005. e5.

[27] Chen Z, Amro EM, Becker F, et al. Coheisin-mediated NF-κB signaling limits hematopoietic stem cell self-renewal in aging and inflammation. J Exp Med 2019;216(1):152–175. doi: 10.1084/jem.20181505.

[28] Coppe JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev Pathol 2010;5:99–118. doi: 10.1146/annurev-pathol-121808-102144.

[29] Reynaud D, Pietras E, Barry-Holson K, et al. IL-6 controls leukemic multipotent progenitor cell fate and contributes to chronic myelogenous leukemia development. Cancer Cell 2011;20:661–673. doi: 10.1016/j.ccr.2011.10.012.

[30] Stifter G, Heiss S, Gastl G, Tzankov A, Stauder R. Over-expression of tumor necrosis factor-alpha in bone marrow biopsies from patients with myelodysplastic syndromes: relationship to anemia and prognosis. Eur J Haematol 2005;75:485–491. doi: 10.1111/j.1600-0609.2005.00553.x.

[31] Rambaldi A, Torcia M, Dinarello CA, Barbui T, Cozzolino F. Modulation of cell proliferation and cytokine production in AML by recombinant interleukin-1 receptor antagonist. Leukemia 1993;7(Suppl 2):S10–S12.

[32] Barreyro I, Will B, Bartholody B, et al. Overexpression of IL-1 receptor accessory protein in stem and progenitor cells and outcome correlation in AML and MDS. Blood 2012;120:1290–1298. doi: 10.1182/blood-2012-01-40699.

[33] Zhang B, Chu S, Agarwal P, et al. Inhibition of interleukin-1 signaling enhances elimination of tyrosine kinase inhibitor-treated CML stem cells. Blood 2016;128:2671–2682. doi: 10.1182/blood-2015-11-679928.

[34] Matatall KA, Jeong M, Chen S, et al. Chronic infection depletes hematopoietic stem cells through stress-induced terminal differentiation. Cell Rep 2016;17:2584–2595. doi: 10.1016/j.celrep.2016.11.031.

[35] Zambetti NA, Ping Z, Chen S, et al. Mesenchymal inflammation drives genotoxic stress in hematopoietic stem cells and predicts disease evolution in human pre-leukemia. Cell Stem Cell 2016;19:613–627. doi: 10.1016/j.stem.2016.08.021.

[36] Preudhomme C, Guilhot J, NicoliSN, et al. Imatinib plus peginterferon alfa-2a in chronic myeloid leukemia. N Engl J Med 2010;363:2511–2521. doi: 10.1056/NEJMoa1004095.

[37] Simonsson B, Gedde-Dahl T, Markevärn B, et al. Combination of pegylated IFN-alpha2b with imatinib increases molecular response rates in patients with low- or intermediate-risk chronic myeloid leukemia. Blood 2011;118:3228–3235. doi: 10.1182/blood-2011-02-336685.

[38] Woolthuis CM, de Haan G, Huls G. Aging of hematopoietic stem cells: intrinsic changes or micro-environmental effects? Curr Opin Immunol 2011;23:512–517. doi: 10.1016/j.coi.2011.03.006.

[39] Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell 2013;153:1194–1217. doi: 10.1016/j.cell.2013.05.039.

[40] Kaufmann E, Sanz J, Dunn JL, et al. BCG educates hematopoietic stem cells to generate protective innate immunity against tuberculosis. Cell 2018;172(1–2):176–190. e19. 11 doi: 10.1016/j.cell.2017.12.031.