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The gut-bone marrow axis: a novel player in HSC aging

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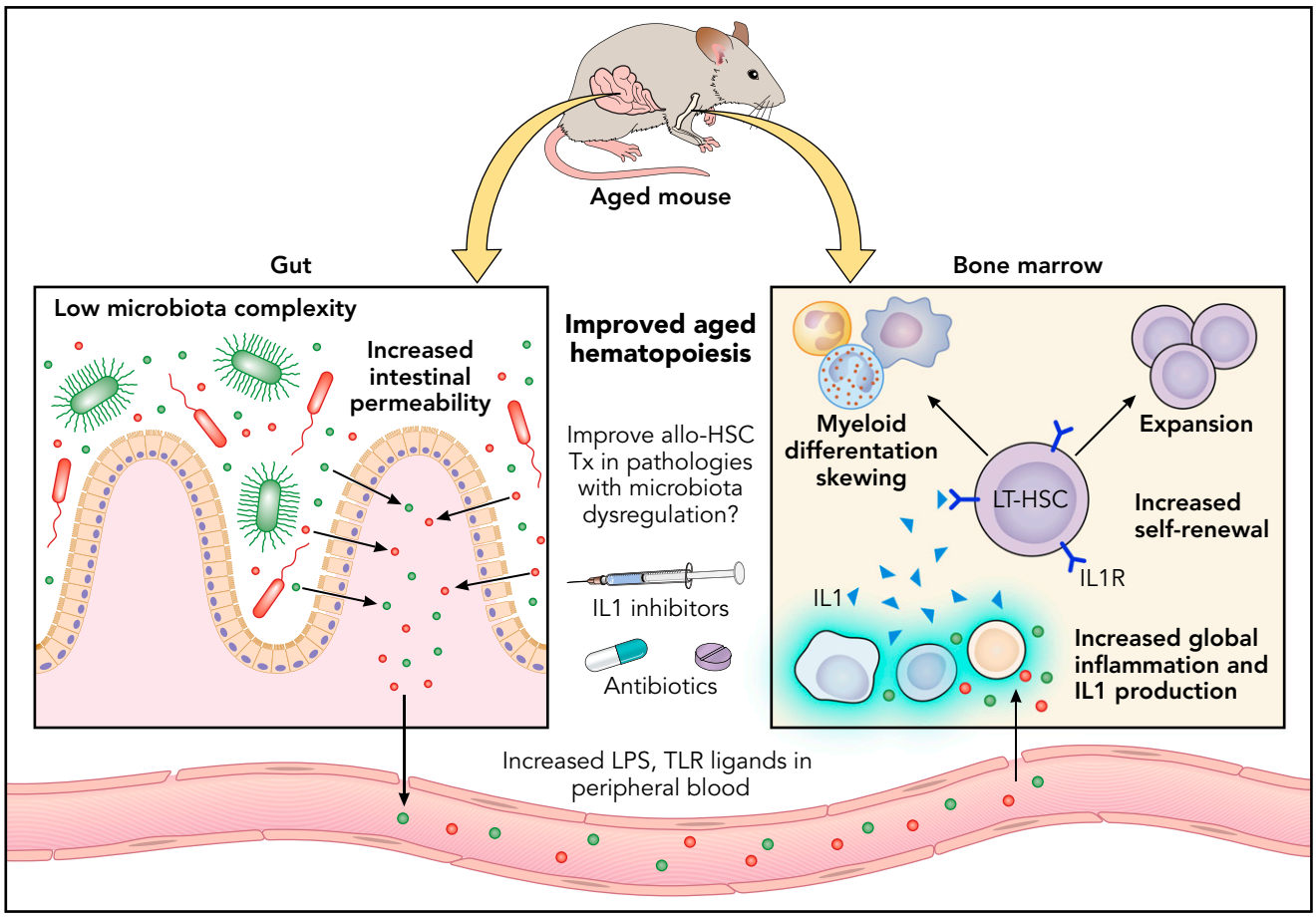
The microbiota is attracting increasing attention for its role in affecting hematopoiesis. In this issue of *Blood*, Kovtonyuk et al describe the role of the microbiome-IL1 axis as a key, self-sustaining, but reversible driver of hematopoietic stem cell (HSC) "inflammaging."[1]

Aging is a very complex physiological process that has been extensively associated with chronic low-grade inflammation, often referred to as "inflammaging," as well as with alterations of the microbiota and increased intestinal leakage. However, the interplay between these phenomena and how they contribute to aging of HSCs was so far not explored. Now, Kovtonyuk et al have described for the first time the role of the microbiome-IL1 axis as a driver of HSC inflammaging.

Alterations of the microbiota and increased intestinal leakage with aging have been previously described both in humans and in mice.[2] Recently, microbiota-derived lactate has been shown to promote hematopoiesis and erythropoiesis by increasing stem cell factor production in leptin receptor$^+$ perivascular cells,[3] highlighting the importance of the functional interplay between intestinal microbiota and the host immune system beyond the gut. Increased levels of interleukin 1a and b (IL-1a/b) with aging impair the function of mature and immature hematopoietic cells, including HSCs. Aged bone marrow (BM) macrophages show higher levels of basal activation and enhanced release of IL1b,[4] which is sufficient for eroding HSC self-renewal capacity and for driving their myeloid skewing.[5] However, what enhances the activation of aged macrophages and triggers this IL-1-dependent low-grade chronic inflammation was so far not explored.



Aging is associated with increased microbial compounds in blood because of increased permeability of the intestinal barrier. Increased levels of microbial compounds in blood stimulate the activation of the IL-1 axis in BM, which drives the HSC myeloid differentiation skewing. The effect on HSCs is IL-1 receptor-dependent and it can be targeted by administration of IL-1 inhibitors or by antibiotic treatment. This gut–BM axis reinforces the importance of the intestinal integrity and the microbiota in allo-HSCT and also as a possible therapeutic target for the aging-related HSC myeloid skewing. Graphics were modified from Servier Medical Art, licensed under a Creative Common Attribution 3.0 Generic License. http://smart.servier.com/.

In this issue of *Blood*, Kovtonyuk et al describe the role of the microbiome-IL-1 axis as a key driver of the HSC myeloid skewing associated with aging. By taking advantage of aged IL-1 receptor 1 knock-out and germ-free mice, they identify alterations in the microbiota composition and bacterial lipopolysaccharide and microbe-associated toll-like receptor ligands release into the aged blood stream as the cause of the increase of IL-1 in the BM and ultimately responsible for the aged-related HSC myeloid skewing. Moreover, they demonstrate that IL-1 receptor 1 expression is necessary for inducing an inflammatory gene signature in aged HSCs in response to increased IL-1 levels (see figure). In aged germ-free mice, the absence of increased IL-1a/b levels, the lack of typical aging hematopoietic traits, the reduced expansion of HSCs and absence of myeloid skewing upon transplantation strongly support a key role for the microbiota in contributing to HSC aging. In addition, microbial compounds are increased in aged mice kept in specific pathogen-free housing condition and lipopolysaccharide stimulation of aged BM cells in vitro and in vivo induces a stronger upregulation of IL-1 compared with the younger counterpart. Inhibition of IL-1 signaling by Anakinra (Kineret, the human IL-1 receptor antagonist) and antibiotic treatment in aged specific pathogen-free mice does not affect the regenerative capacity of HSCs but improves the myeloid skewing, restoring balanced differentiation. These results imply the microbiota and microbiota-induced changes are novel players in the regulation of HSC aging.

The demonstration of a direct effect of the microbiota and of microbiota-derived molecules on HSCs forces us to extend our definition of the HSC niche and the source of HSC regulatory molecules. More generally speaking, the gut–BM axis may represent the starting point for new therapeutical approaches and to refine and improve currently available clinical protocols. For example, allogeneic HST transplantation (allo-HSCT) is one of the current strategies to ameliorate different neurological and autoimmune diseases in which the microbiota has been found altered, such as multiple sclerosis.[6] The precise mechanisms involved in the beneficial effect of HSCT are not yet known. Furthermore, dysbiosis, a disruption of the microbiome natural balance, is a known cause of serious health problems and, in general, patients undergoing allo-HSCT often experience significant alterations in their microbiota[7] because of their underlying malignancies, exposure to extensive chemotherapy, and systemic antibiotics.[8] The evidence provided by Kovtonyuk et al may suggest that the introduction of a new hematopoietic system not exposed to an altered microbiota could be associated with the improvement in disease progression. This construct supports exploring a new therapeutic approach, concurrently targeting the microbiota or IL-1 signaling as important complementary treatments for these pathologies. As a more immediate consequence, dietary control and manipulation could be a promising approach to preserve intestinal function (microbiota complexity and intestinal permeability) and consequently to prevent the functional decline of the immune system with aging.

Inflammaging plays a role in aging of different tissues beside the hematopoietic system. This direct connection of aging-related intestinal leakage and released of microbial compounds in the blood stream with HSCs suggests that similar interactions for other somatic stem cells and tissues could be explored. It would be intriguing to test if IL-1 inhibition or antibiotic treatment affect directly or indirectly other stem cell compartments, promoting the reversal of their age dependent functional impairment.

Despite the importance of the microbiome–IL-1 axis highlighted in this work in driving extrinsic HSC aging, intrinsic stem cell aging cannot be ignored. IL-1 inhibition strongly reduces HSC myeloid differentiation skewing; however, this intervention fails to restore an engraftment level equal to the one of young donor mice. In line with this observation, it was recently demonstrated that aged HSCs are refractory to bloodborne systemic rejuvenating interventions.[9] Therefore, these data point out the complexity of stem cell aging and the existence of an intrinsic component of HSC aging that remains independent from the extrinsic regulation of the niche. Most likely, only a combined approach targeting both intrinsic and extrinsic aspects of stem cell aging will be needed as an effective strategy to rejuvenate HSCs and possibly affect aging of the whole organism.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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