# Can molecular targeting the TNFα-ERK-ETS1-IL27Rα pathway keep us young and healthy by protecting HSCs from aging?

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The world's older population grows at an unprecedented rate. Today, there are about 8.5% of people worldwide (617 million) aged 65 and older today, which is projected to continue growing to nearly 17% of the world's population by 2050 (1.6 billion). World population aging has profound implications because aging represents a progressive deterioration of physiological function accompanied by an increase in vulnerability for disease and mortality. Although aging itself is not a disease, it is the greatest risk factor for most chronic human diseases, including cardiovascular and neurodegenerative disease, cancer, diabetes, and osteoarthritis; and a major contributing factor for the increased susceptibility to various infectious diseases such as COVID-19. Age-related changes in the hematopoietic and immune system likely play an important role in the pathogenesis of these diseases in part via induction of immunosenescence and inflammaging.[1] These changes have been largely attributed to hematopoietic stem cell (HSC) aging, which leads to a significant decline in HSC self-renewal and long-term hematopoietic reconstitution, a myeloid skewing (ie, increase in myeloid cell but decrease in lymphoid cell production), and clonal hematopoiesis and increased hematological malignancies.[2] Both cell-intrinsic and cell-extrinsic alterations have been implicated in driving HSC aging. The cell-intrinsic mechanisms of HSC aging include increased DNA damage,[3] loss of polarity and proteostasis,[4] impaired autophagy and mitochondrial activities,[5] epigenetic reprogramming and senescence.[6,7] The cell-extrinsic mechanisms are less studied but may include alterations in bone marrow stromal cell populations, changes in the production of hematopoietic stimulators (such as osteopontin) and inhibitors (such as CCL5) by the stromal cells, and increased production of inflammatory cytokines.[8] However, how these cell-extrinsic factors communicate with HSCs to promote HSC aging has not been well established.

In a recent Blood publication,[9] Dr. Jianwei Wang's group investigated the mechanistic link between age-related inflammation and HSC aging. They found that aging is associated with an upregulation of interleukin 27 receptor α (IL27Rα) expression in HSCs from mouse bone marrow, resulting in a significant expansion of IL27Rα$^+$ HSCs. IL27Rα$^+$ HSCs from both young and old mice exhibited all the phenotypes of aged or senescent HSCs, including inability to self-renew, produce long-term hematopoietic reconstitution, and differentiate into both myeloid and lymphoid cells in a balanced manner after transplantation. In contrast, IL27Rα$^-$ HSCs from both old mice and HSCs from old IL27Rα knockout (IL27Rα$^{-/-}$) mice exhibited significant improvement in HSC functions compared to IL27Rα$^+$ HSCs from the same aged mice. These findings indicate that IL27Rα can be used as a biomarker for aged and senescent HSCs. Next, they investigated the underlying mechanisms contributing to the age-related upregulation of IL27Rα in HSCs. They found that NF-κB and EST1 are important transcription factors that regulate the expression of IL27Rα. However, aging is associated with an increased expression of phosphorylated ERK and ETS1 in HSCs, but with no changes in the NF-κB activation. The activation of the ERK-ETS1 pathway and increased expression of IL27Rα in old HSCs may be attributable to the stimulation by the HSC-extrinsic proinflammatory cytokine TNFα. This is because mouse bone marrow plasma from old mice contained a significantly higher level of TNFα than that from young mice. TNFα stimulated the expression of IL27Rα in c-Kit$^+$ Sca1$^+$ Lineage$^-$ (KLS) cells and HSCs in vitro and in vivo, respectively, in an ETS1-dependent manner. The upregulation of IL27Rα in HSCs is likely responsible for mediating TNFα-induced HSC dysfunction because knockout IL27Rα could prevent TNFα-induced HSC dysfunction. Therefore, these findings are highly significant by providing the first link between cell-extrinsic and cell-intrinsic communications that lead to HSC aging via the activation of the TNFα-ERK-ETS1-IL27Rα pathway. It will be of great interest to determine whether molecular targeting this pathway with a small molecule inhibitor or an antibody has the potential to be developed as a novel therapeutic strategy to slowdown HSC aging, which may lead to reduced inflammaging and improvement of hematopoietic and immune functions, particularly under various age-related pathological conditions in which TNFα production is upregulated systemically or locally in the bone marrow microenvironment. However, cautions have to be take into consideration before translating this approach into the clinic because IL27Rα$^+$ HSCs may be primarily responsible for emergency hematopoiesis in the fight against bacterial infection as shown by the authors in this publication.

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