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POSTER ABSTRACTS

506.BONE MARROW MICROENVIRONMENT

Reduction in Lymphoid-Supporting Factors By Mesenchymal Stromal Cells Drives Myeloid-Biased Hematopoiesis at Middle Age

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The bone marrow "niche" for hematopoietic stem cells (HSCs) encompasses various cell types, extracellular matrices and secreted factors that maintain the specialized functions of HSCs such as quiescence, self-renewal, and production of multipotent progenitor cells. In old age, changes in this niche contribute to dysfunction of HSCs and the hematopoietic system including increased inflammation and myeloid-biased molecular programs. We have observed that HSC and hematopoietic aging phenotypes become apparent by mid-age (Young et al. *Cell Stem Cell* 2021, Young et al. *J Exp Med* 2016), leading to the hypothesis that evaluating alterations in the niche at this stage would reveal the earliest changes initiating HSC aging. To test this hypothesis, we examined both the hematopoietic and non-hematopoietic compartments in individual middle-aged (12-14 months of age, $n = 9$) and compared them to young C57BL/6 mice (2-4 months of age, $n = 5$). Immunostaining of femurs showed an increase in sinusoid volume, vessel dysmorphia, and an increase in megakaryocyte abundance in the bone marrow of middle-aged mice. No alterations were observed in arterioles nor adipocyte volume. This data provides supporting evidence that a subset of HSC niche remodeling phenotypes observed in old age are present by mid-age. We then performed single-cell RNA-seq to comprehensively assess changes in abundance and transcriptomes of hematopoietic and non-hematopoietic cells at mid-age. Analysis of this data revealed significant expansion of HSCs in middle-aged mice. In the expanded HSC population, a reduction in B lymphoid differentiation signatures was observed without alterations in inflammation or myeloid differentiation signatures. Computational predictions suggested that the reduced B lymphopoiesis program in middle-aged HSCs resulted from decreased interaction with soluble factors produced by subsets of mesenchymal stromal cells (MSCs), rather than endothelial cells or other hematopoietic cell compartments. Specifically, reduced MSC-to-HSC interactions were linked to a decline in signaling mediated by adiponectin (ADIPOQ; *Adipoq*), stem cell factor (SCF; *Kitl*), midkine (MDK; *Mdk*), and insulin-like growth factor 1 (IGF1; *Igf1*). Among these, reductions in *Kitl* and *Igf1* in MSCs were correlated with the loss of B lymphopoiesis programs in HSCs comparing individual middle-aged mice. To test the functional impact of the decline in *Igf1* in MSCs on lymphopoiesis, we created three MSC-selective *Igf1* conditional knockout mouse models using distinct Cre recombinases (Lepr-Cre, nestin-CreER and Prx1-CreER). In all three of these models, MSC-selective knockout of *Igf1* reduced B lymphopoiesis resulting in myeloid-biased hematopoiesis, replicating hematopoietic aging phenotypes observed at middle age. These findings indicate that the decline in B lymphopoiesis from HSCs during aging is initiated by a reduction in lymphoid-supporting factors produced by MSCs in the bone marrow microenvironment, and this occurs independently of inflammation or activation of myeloid-promoting transcriptional programs in HSCs.

Disclosures No relevant conflicts of interest to declare.

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