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POSTER ABSTRACTS

506.BONE MARROW MICROENVIRONMENT

NFκB Dysregulation in the Bone Marrow Niche Drives Epigenomic Reprogramming of Hematopoietic Stem Cells and Myeloid Bias

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Introduction
Aging and chronic inflammation are known to skew hematopoietic output by favoring myelopoiesis and disfavoring lymphopoiesis. In addition, the bone marrow niche plays critical roles in supporting steady-state hematopoiesis, and alterations in the microenvironment may similarly influence disordered hematopoiesis. The NFkB system is a central, pleiotropic regulator of inflammatory signaling in many cell types. Thus, we reasoned that experimental perturbations of NFκB signaling may be used to study how inflammatory dysregulation affects hematopoiesis.

Methods
We generated a mouse model of inflammatory immune dysregulation, the IκB $^{-}$ mouse (*Nfkbia* $^{+/-}$ *Nfkbib* $^{-/-}$*Nfkbie* $^{-/-}$), and then compared the peripheral blood and bone marrow inflammatory proteins and cell compositions betweenyoung WT, young IκB $^{-}$,and aged WT mice. Using bone marrow transplantation, we next assayed the effect of an inflamed IκB $^{-}$ recipient niche on the hematopoietic output of WT donor bone marrow. Finally, we performed single cell RNA sequencing (scRNA-seq) and assay for transposase-accessible chromatin sequencing (ATAC-seq) on sorted hematopoietic stem and progenitor cells (HSPC) to characterize the epigenomic and transcriptional changes occurring in WT HSPC from an immune dysregulated environment.

Results
We observed an increase in inflammatory cytokines in both young IκB $^{-}$ and aged WT mice compared to young WT controls, as well as myeloid bias in the peripheral blood leukocytes and bone marrow HPSC. Transplantation studies showed that inflammatory dysregulation in the radio-resistant microenvironment resulted in myeloid-biased hematopoiesis. However, this myeloid bias was lost upon secondary transplantation of bone marrow into a WT recipient. Performed on HSPC from an inflamed microenvironment, our scRNA-seq studies showed myeloid bias at the transcriptional level, and ATAC-seq studies further revealed epigenomic changes, with an increased transcription factor (TF) binding motif accessibility for myeloid-priming TFs in long term HSC.

Conclusions
Our studies establish the IκB $^{-}$ mouse as a new model of chronic inflammatory dysregulation that can be used to study the effects of an inflamed bone marrow microenvironment on hematopoiesis. Furthermore, our findings indicate that dysregulated NFκB signaling in the bone marrow microenvironment leads to myeloid bias in HSPC, and is associated with epigenomic reprogramming at the stem cell level. However, despite this epigenomic reprogramming, we observed that myeloid bias could be reversed upon bone marrow re-transplant into a non-dysregulated niche. Together, these data suggest that further understanding niche-derived inflammatory dysregulation may be a useful in targeting disordered hematopoiesis in chronic inflammatory states such as aging.

Disclosures Rao: *AbbVie, Inc:* Consultancy, Speakers Bureau.

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