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POSTER ABSTRACTS

501.HEMATOPOIETIC STEM AND PROGENITOR CELLS AND HEMATOPOIESIS: BASIC AND TRANSLATIONAL

Detection and Prevention of ADAR1p150-Induced Hematopoietic Stem and Progenitor Cell Aging

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Introduction: Over the last decade, ADAR1p150 has been linked by our research team and others to malignant progenitor reprogramming and therapeutic resistance in a broad array of malignancies. However, ADAR1p150's role in accelerated hematopoietic stem and progenitor cell (HSPC) aging in response to inflammatory cytokines had not been clearly elucidated. Here, we investigate ADAR1 splice isoform switching and the ADAR1p150 inhibitory effects of Rebecsinib on human HSPC function in normal humanized aged normal bone marrow (aNBM) HSPC mouse models.

Methods: Whole transcriptome RNA sequencing (RNA-seq) was utilized with splice isoform and editome analysis to detect ADAR1 splice isoform switching and adenosine to inosine RNA editing. Rebecsinib (17S-FD-895), a pre-IND drug candidate, has shown promising potential as an inhibitor of ADAR1p150-mediated RNA editing (*Crews, Ma...Jamieson. Cell Stem Cell 2023*), which is an important therapeutic target in patients with myelofibrosis or acute myeloid leukemia that overexpress ADAR1p150 compared with ADAR1p110. Human CD34 $^{+}$ cells, isolated from aged normal bone marrow (aNBM) from patients undergoing elective hip replacement surgery, were transduced with a lentiviral ADAR1-nano-luciferase reporter and transplanted into NSG-SGM3 adult mice that secrete human SCF, IL-3, and GM-CSF cytokines that support normal hematopoiesis. After engraftment confirmation peripheral blood human CD45 flow cytometric assessment and IVIS 200 system imaging of ADAR1-nano-luc-GFP reporter expressing HSPC engraftment, the mice were randomly divided into vehicle-treated and Rebecsinib-treated groups (15mg/kg, twice a week for two weeks). Peripheral blood, bone marrow, and spleen were collected upon treatment completion for analysis.

Results: By HSPC RNA-seq, we detected an imbalance between ADAR1p150 and ADAR1p110 expression together with increased RNA editing and splicing alterations using whole transcriptome RNA sequencing (RNA-seq) of aged compared with young bone marrow hematopoietic stem and progenitor cells (HSPCs). However, the functional relevance of ADAR1 splice isoform switching had not been evaluated in human-aged normal bone marrow HSPC xenograft (PDX) mouse models nor had this cytokine-induced HSPC aging been reversed. Flow cytometric analysis and immunohistochemistry staining revealed that Rebecsinib treatment at a dose of 10mg/kg, twice a week for two weeks, effectively spared normal human immune cells (CD3+, CD14+, and CD19+ cells). Remarkably, Rebecsinib treatment not only preserved Hematopoietic Stem (CD34+CD38-) cells and Progenitor (CD34+CD38+) cells in peripheral blood, bone marrow, and spleen but also promoted their expansion. These findings demonstrate the potential of Rebecsinib to enhance the retention of HSPC populations in the bone marrow niche.

Conclusions: Our pre-clinical experiments utilizing RNA-seq, a novel ADAR1-nano-luciferase-GFP reporter, and aNBM PDX mouse models provide compelling evidence supporting the potential of Rebecsinib to restore the balance of ADAR1p150:p110 ratios and engraftment in humanized aNBM HSPC mouse models. These findings highlight Rebecsinib as a promising therapeutic candidate for targeting leukemia and myelofibrosis while preserving essential HSPC populations.

Disclosures No relevant conflicts of interest to declare.

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