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

Title: MLLT1 Is Required to Maintain Normal B-Lineage Hematopoiesis and Mitochondrial Function

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MLLT1 (aka ENL) is an epigenetic reader protein that binds to crotonylated/acetylated lysine residues of histone 3 through its N-terminal YEATS domain. Multiple different positive and negative regulatory complexes compete for binding to the MLLT1 C-terminal domain. MLLT1 has been implicated in leukemic stem cell survival in *MLL*-rearranged cell lines but its role in normal hematopoiesis has not been investigated. *Mllt1* is expressed in multiple bone marrow cell subsets, with high expression levels in multipotent and B-lineage progenitors. We generated conditional *Mllt1* knockout (*Mllt1* ^{del}) mice and observed a B-lineage defect in bone marrow of *Mllt1* deleted mice compared to control *Mllt1* $^{fl/fl}$ mice. Mitochondrial activity has been linked to hematopoietic lineage fate decision choices. We performed seahorse mitochondrial stress test on lineage negative (stem and progenitor) bone marrow cells and found that lineage negative cells of *Mllt1* ^{del} mice have lower mitochondrial activity (as a measure of oxygen consumption rate) than control *Mllt1* $^{fl/fl}$ mice. In addition, we observed mitochondrial mass (as a quantitative measure of ratio of mtDNA gene *CytB* / nDNA gene *ActB*) to be decreased in lineage negative cells of *Mllt1* ^{del} mice when compared to control *Mllt1* $^{fl/fl}$ mice. Surface marker labeling was used to sort more defined subpopulations from bone marrow of *Mllt1* ^{del} and *Mllt1* $^{fl/fl}$ mice. We observed decreased mitochondrial mass in MPP4s and MEPs of *Mllt1* ^{del} mice when compared to control *Mllt1* $^{fl/fl}$ mice. Flow cytometry-based cell surface labeling to distinguish different bone marrow progenitors, plus mitochondria staining using MitoTracker Green (for mitochondrial mass) and MitoTracker Red CMXRos (for mitochondrial membrane potential) showed altered mitochondrial function of B-lineage progenitors in *Mllt1* ^{del} mice when compared to control *Mllt1* $^{fl/fl}$ mice. Thus, Mllt1 is essential for normal mitochondrial function, which may be necessary to maintain specific bone marrow hematopoietic subpopulations. Ongoing studies include gene expression profiling of sorted lymphoid progenitor populations and analysis of direct Mllt1 target genes that contribute to the altered phenotype in *Mllt1* ^{del} mice.

Disclosures No relevant conflicts of interest to declare.

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