Different hematopoiesis and response to 5-azacytidine treatment in Tp53 mutation mice

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TP53 R172H missense mutation and deletion are highly occurred in patients with myelodysplastic syndrome (MDS), the most common adult myeloid malignancy. In order to study the role of *TP53* mutation in hematological system, we used four mouse models carrying *Tp53* mutation including *Tp53* R172H missense mutation (R172H/WT and R172H/R172H) and *Tp53* deletion mice (*Tp53*+/- and *Tp53*-/-). We characterized the hematopoiesis and studied the blood chimerism after 5'-Azacytidine (AZA) treatment in these mouse models. *Tp53* R172H missense mutation mice have a minor reduction in myeloid-erythroid progenitors (MEP) compared to wide type (WT) mice. *Tp53*+/- and *Tp53*-/- mice have a higher percentage of hematopoietic stem cells (HSC) and lineage-/Sca+/Kit+ bone marrow (BM) progenitor cells (KLS) compared to WT mice. Competitive BM repopulation transplant studies showed that stem cells from all four *Tp53* mutation mouse models have a competitive advantage over WT competitor stem cells, with *Tp53*-/- stem cells having the largest advantage based on peripheral blood chimerism. BM cells from donor (CD45.2 *Tp53* mutation mice) and competitor (CD45.1 WT mice) were mixed and competitive repopulation assays were performed followed by AZA treatment. The *Tp53*-/- mice have a competitive disadvantage after AZA treatment compared to PBS treatment, in which inhibition of T cell development and maturation mostly contributes to the phenotype observed. Our studies showed that *Tp53* mutation affects hematopoiesis in mice. Inhibition of T cell development and maturation by AZA may be a mechanism for the effectiveness of AZA in treating MDS patients carrying *Tp53* deletion.

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