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

Tuoen Liu
West Virginian School of Osteopathic Medicine, USA

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’-Azacitidine (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.

tlieu@osteo.wvsom.edu