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POSTER ABSTRACTS

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

The Effect of SCD-1 Inhibition on Human Hematopoietic Stem Cell Mitochondrial Metabolism, Cell Proliferation, and Differentiation Potential

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Hematopoietic stem cells (HSC) give rise to all blood lineages and sustain the production of blood cells throughout life. Due to their inherently high regenerative potential, HSC are used in a variety of clinical settings, including bone marrow transplantation (BMT) directly to cure a variety of hematologic and oncologic disorders often with gene therapy. During regeneration, HSC are activated into cycle. For this, HSC undergo drastic mitochondrial and metabolic remodeling to meet the bioenergetic and biosynthetic needs of activated HSC. A growing body of evidence indicates that HSC sustain injury during activation. This remodeling is important for optimal HSC function but is permanently changed after HSC activating stress. It is thus important to identify the metabolic needs of activated HSC to improve HSC functions for therapeutic purposes. In both murine and human HSC, numerous metabolic enzymes get upregulated during activation, including those involved in de novo lipid synthesis. This metabolism is poorly understood in human HSC. Our overarching question is to understand the metabolic needs of HSC within the human system.

Stearoyl-co-A-desaturase 1 (SCD-1), an enzyme responsible for conversion of stearic to oleic acid within the de novo lipid synthesis pathway, is suspected to play a role in metabolic reprogramming after stress. Using CD34+ mobilized human peripheral blood, we analyzed the effect of SCD-1 inhibition on HSC and progenitor proliferation, mitochondrial metabolism, and lineage differentiation potential. Cells were cultured either in vehicle control conditions or with SCD-1 inhibitor (SCDi). Subsequently, cells were counted and analyzed by flow cytometry on Days 4-5 and 10-15. More primitive or stem cell markers were utilized on Days 0 and 5 whereas differentiation markers were utilized on Day 10-15. Both tetramethylrhodamine-ethyl ester dye (TMRE) and MitoSOX reagents were used to assess mitochondrial membrane potential and mitochondrial ROS, respectively. Our results demonstrate that the size of the HSC population generated by SCDi-treated CD34+ cells within 5 days of culture was similar to vehicle treated cells and was composed of similar proportion of CD34+CD38+, CD34+CD38-, and CD38+CD34- cells, indicating that SCD-1 inhibition does not alter HSC expansion under these culture conditions. However, TMRE levels were lower in all HSC populations whereas mitoSOX levels were unchanged by SCD-1 inhibition compared to vehicle. In differentiation conditions, SCDi cultures were composed of a larger proportion of myeloid progenitors and a smaller proportion of erythroid cells after 10-15 days, compared to vehicle-treated cultures. These findings suggest that de novo lipid synthesis is necessary for HSC differentiation but dispensable for proliferation/expansion in vitro.

We then used a xenotransplant model to assess the effect of SCDi on HSC regenerative potential in vivo. CD34+ mobilized human peripheral blood cells were cultured for 3 days under conditions that maintain HSC functions in vitro and transplanted into immunodeficient, sublethally irradiated NSG mice. Peripheral blood of xenotransplanted mice was analyzed monthly for human cell chimerism and mature blood lineage potential from 1 to 6 months post-transplant. Bone marrow analysis was performed at the 6 month time point as well, assessing for both HSC markers and lineage markers. Mice that received SCDi-treated cells exhibited human cell chimerism at a level similar to mice that were transplanted with vehicle treated cells, at about 3 to 30%. However, SCDi-treated cells gave rise to a lymphoid-biased graft, in particular T cells, both in the peripheral blood and in the bone marrow of xenotransplanted mice, compared to a more balanced myeloid-lymphoid graft from vehicle treated cells.

In conclusion, these findings suggest that de novo lipid synthesis is critically important for HSC lineage fate and balanced differentiation in vitro and in vivo. This is especially clinically relevant as this work may implicate a possible therapeutic target as improving de novo lipid synthesis may aid in patients who suffer from persistent cytopenias after BMT and graft failure.

Disclosures No relevant conflicts of interest to declare.

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