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POSTER ABSTRACTS

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

Decline in Cardiolipin in Hematopoietic Stem Cell during Aging Alters Their Regenerative Potential

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Hematopoietic Stem Cells (HSCs) are known for their regenerative potential. This property allowed the use of HSC in bone marrow transplantation to treat hematological disorders such as leukemia. However, aging influences these characteristics of HSCs. The major hallmarks of aging are limited self-renewal and reconstitution capacity resulting in HSC exhaustion in aged individuals. Mitochondrial metabolism and activity are active drivers of HSC fate decisions and data from our lab shows that mitochondria in aged HSCs have increased sphericity with a polarized mitochondrial network and a lower mitochondrial membrane potential. An important aspect of mitochondrial functions is the lipid composition of their membranes. A lipid trafficking assay showed an atypical pattern of lipid incorporation by mitochondria in aged HSCs suggesting that mitochondrial lipids become abnormal upon aging. The overall content of Cardiolipin (CL) which is a signature mitochondrial lipid, found exclusively in the inner mitochondrial membrane was also reduced during aging. This was done with flow cytometry using a CL marker NAO (Non-Acridine Orange). Tafazzin encoded by the gene TAZ is crucial for remodeling CL into its mature form which is required for maintaining mitochondrial functions. Mutations in the TAZ gene have been known to cause a reduction in the synthesis of mature CL which is often associated with HSCs functional defect. Western Blot analysis showed a considerable decrease in Taz protein expression in aged stem and progenitor cells (HSPC) compared to young HSPC. To understand the effect of reduced Taz expression on HSC functions, we used a doxycycline inducible, sh-RNA mediated TAZ knock-down (KD) mouse model. Bone marrow analysis indicates that the frequency of HSC and multipotent progenitors decreases significantly in 6-month-old TAZ KD mice compared to wild type (WT) mice. Our data shows that following 5FU induction TAZ KD mice have a significant reduction in the multipotent progenitor and HSC population on day 10 and day 21 post 5FU, indicating TAZ KD decrease the regenerative potential of HSCs under stress conditions. Further pointing towards the significance of cardiolipin in HSC regeneration. TAZ KD mice also have abnormal peripheral blood recovery post 5FU mainly affecting the platelets.

We next examined the repopulation potential of HSCs isolated from TAZ KD mice using serial competitive transplantation assays. While primary transplanted mice of TAZ KD HSCs exhibited similar donor-cell chimerism compared to mice transplanted with WT HSCs, about 50-60%, secondary recipient of TAZ KD cells had significantly lower donor-cell chimerism than secondary recipients of WT cells. Further, donor-derived HSC frequency in the bone marrow of recipients of TAZ KD HSCs 24 weeks following engraftment was also significantly lower than recipients of WT HSCs. Hence, Taz-deficiency causes a defect in HSC self-renewal under regenerative conditions.

We next evaluated whether restoring cardiolipin levels in mid-aged HSCs could rescue their functions. For this, mid-aged HSC were incubated for 3 days under conditions that maintain HSC functions in vitro with Alcar (Acetyl-L-Carnitine), which promotes CL production. In lipid incorporation assay, Alcar supplementation restored mitochondrial membrane potential, mitochondrial organization and lipid incorporation of mid-aged HSCs. In competitive transplant assay, while mid-aged WT HSC treated with vehicle gave rise to a myeloid-bias graft, Alcar supplemented mid-aged WT HSC gave rise to a more balanced graft with increased ratio lymphoid to myeloid cells in the peripheral blood 16 weeks following transplantation, albeit the rescue was partial.

This study indicates that HSC mitochondrial membrane lipids become abnormal with aging which causes a decline in HSC function and highlights the critical role of mitochondrial cardiolipin in HSC functions. It implies that metabolite supplementation is a viable option for restoring age-related HSC functional defects.

Disclosures No relevant conflicts of interest to declare.

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