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POSTER ABSTRACTS

506.BONE MARROW MICROENVIRONMENT

Notch Signaling Is Required for Extramedullary Hematopoiesis in the Adult Liver

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During embryonic development, hematopoietic stem cells (HSC) in the fetal liver undergo expansion and self-renewal. Fetal HSCs migrate to the bone marrow (BM) niche towards birth and remain there during adulthood. Extramedullary hematopoiesis (EMH), or hematopoiesis outside of the BM, predominantly occurs in the fetal liver or when the adult BM niche ceases to be a site for functional hematopoiesis. The mechanism by which the adult liver becomes reactivated as a site of EMH for itinerant HSCs is unknown. Our project is investigating EMH in the adult liver by inducing acute hemolytic anemia in adult mice that induces egress and homing of hematopoietic progenitors to the liver and spleen. Our work demonstrates that long-term HSCs isolated from the portal vein in the adult liver can serially reconstitute lethally irradiated mice. Thus, the adult liver serves as a potential reservoir for long-term, functional HSCs in the presence of a damaged BM niche. In pursuit of a mechanism, we focused on Notch-signaling which is an evolutionarily conserved pathway that has been shown to play a critical role in HSC emergence and fetal liver development. When comparing WT liver donors to Notch-deficient (Notch1 $^{+/\Delta TAD}$) or Notch knockout (Notch1 ^{ff}VavCre $^{+}$) liver donors, hematopoietic transplants reveal that Notch mutant progenitors fail to efficiently reconstitute irradiated recipients. Using an HSC-specific a-catulin-GFPmouse model, we are able to track the expression of GFP $^{+}$ liver-originating HSCs after hematopoietic reconstitution. We show that mice reconstituted by EMH-activated a-catulin-GFP liver HSCs are able to provide long-term reconstitution in lethally irradiated recipients and resume residence in the bone marrow niche of recipients. Additionally, we see distinct localization of GFP $^{+}$ HSCs localized near sinusoids throughout the EMH liver niche using whole-mount imaging. We have validated receptor-ligand binding interactions of the Notch1 receptor with ligand-expressing hematopoietic cells in the adult liver. Using intracellular flow cytometry after EMH in the adult liver, we see a 3-fold increase in mean fluorescent intensity of GATA2 in HSPCs (hematopoietic stem cell progenitors) when compared to our bone marrow and isotype control mice. We demonstrate that Notch-driven GATA2 expression is a crucial regulator of self-renewal and functional maintenance of stemness during EMH of HSCs in the adult liver. Our findings reveal a developmentally conserved Notch signaling mechanism is reactivated in the adult liver to retain the functional potential and maintenance of HSCs as they adapt to inhospitable conditions in the bone marrow niche.

Disclosures No relevant conflicts of interest to declare.

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