Itaconate-mediated regulation of hematopoietic stem and progenitor cell fate

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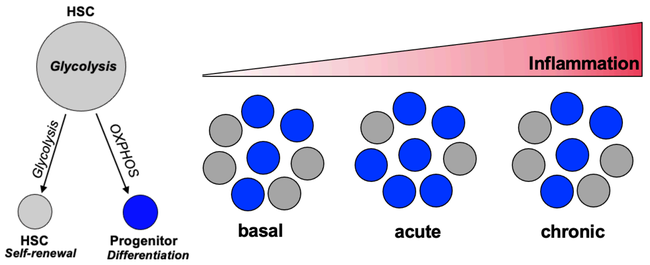
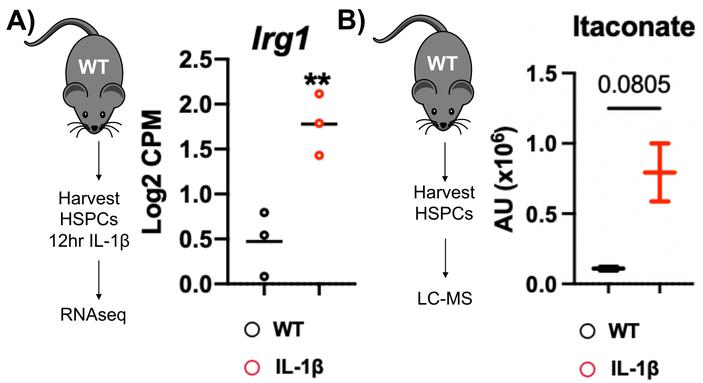
Background



- Hematopoietic stem and progenitor cells (HSPCs) replenish all lineages of blood cells over an organism's lifetime
- Under inflammatory conditions like blood system development or autoimmune disease, HSC undergo a metabolic switch from glycolysis to OXPHOS, promoting differentiation
- However, lethal depletion of HSC does not typically occur in these scenarios implying the existence of mechanisms that prevent HSC exhaustion during stress.

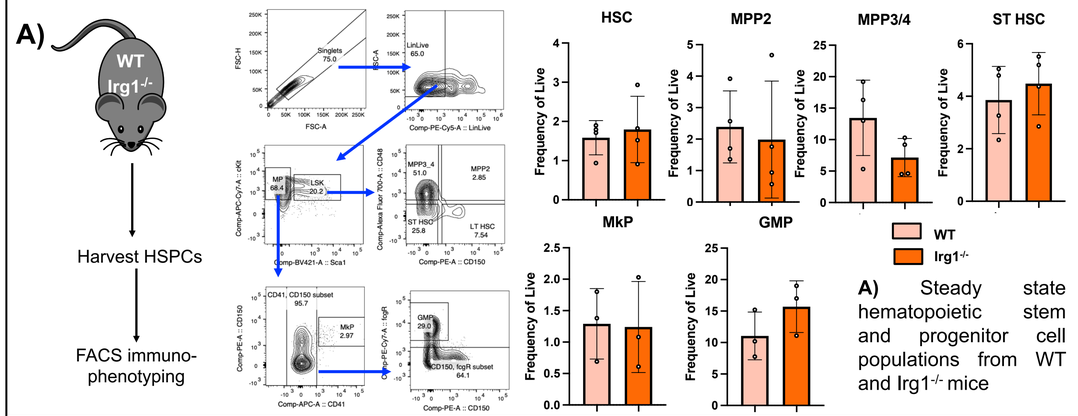
We hypothesize that HSC elicit a secondary metabolic program that breaks inflammation-driven OXPHOS to prevent differentiation and subsequent exhaustion

IL-1β induces itaconate in cKit+ HSPCs



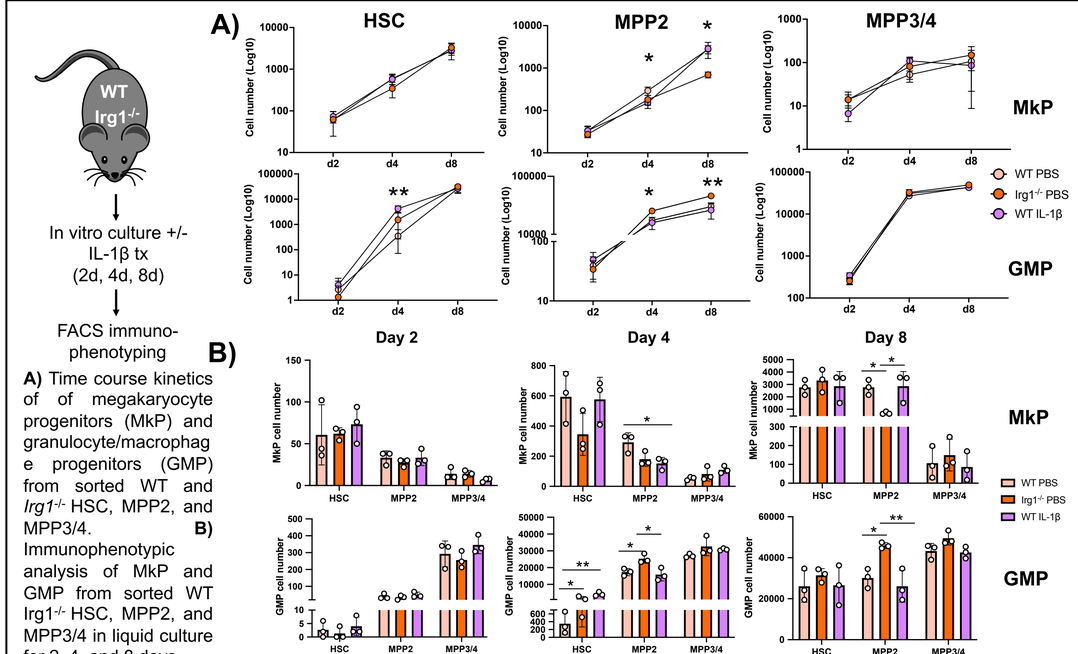
A) *Irg1* transcript levels from *ex vivo* WT HSPCs RNAseq **B)** *Ex vivo* metabolite levels from WT HSPCs **C)** FACS immunotyping from ex vivo WT and *Irg1* KO HSPC

Steady state hematopoiesis is preserved in *Irg1* deficient mice



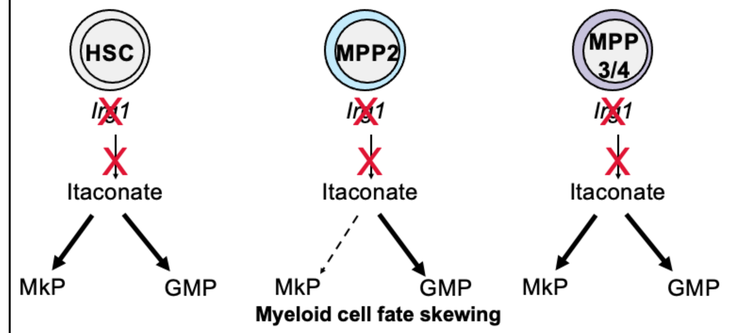
A) Steady state hematopoietic stem and progenitor cell populations from WT and Irg1$^{-/-}$ mice

Itaconate drives myeloid cell fate choice in liquid culture



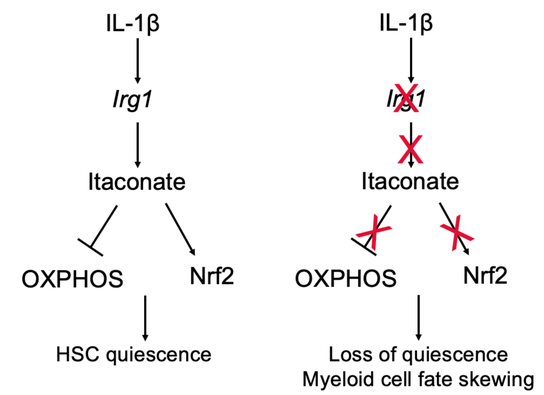
A) Time course kinetics of of megakaryocyte progenitors (MkP) and granulocyte/macrophage progenitors (GMP) from sorted WT and *Irg1*$^{-/-}$ HSC, MPP2, and MPP3/4. **B)** Immunophenotypic analysis of MkP and GMP from sorted WT Irg1$^{-/-}$ HSC, MPP2, and MPP3/4 in liquid culture for 2, 4, and 8 days

Conclusions



- Loss of endogenous itaconate alters the composition of HSPCs in *Irg1* KO mice
- Ablation of itaconate synthesis in multipotent progenitor cells skews MPP2 output in favor of myeloid cells

Future Directions



- Itaconate is a competitive inhibitor of succinate dehydrogenase (SDH) and leads to the stabilization of the anti-inflammatory transcription factor Nrf2
- To elucidate the mechanism by which itaconate regulates HSPC fate, assays incorporating a combination of inhibition via pharmacologic inhibitors and/or shRNA knockdown will be employed