AB038. Pathological neovascularization in retinopathy of prematurity is regulated by heme-derived iron trafficking

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Background: Retinopathy of prematurity (ROP) is an eye disease of the immature newborn characterized by pathological neovascularization (NV). ROP classically arises due to changes in oxygen availability in the retina. However, other factors, such as red blood cell (RBC) transfusion, independently contribute to disease severity. Heme molecules, rich in RBC, are the primary source of endogenous iron. Heme is metabolized by heme oxygenase (HO) into biliverdin, carbon monoxide, and ferrous ions. Low iron levels stabilize hypoxia-inducible factor 1α (HIF1 α), the main transcription factor of vascular endothelial growth factor (VEGF) that drives angiogenesis. Here we investigate the role of heme metabolism in pathological NV.
Methods: ROP was studied using the well-characterized oxygen-induced retinopathy (OIR) mouse model. Wild-type (WT) pups are exposed to high oxygen concentrations (FiO2 75%) for 5 days, from the post-natal day (P) 7 to 12, and subsequently returned to room air until retinal collection at P12, P14, & P17. Retinas are then analyzed via single-cell RNAseq, RT-qPCR, western blot, Prussian blue staining, and immunostaining techniques to elucidate the effect of OIR on iron metabolism and Hmox1. In OIR, we quantified vaso-obliteration (VO) and pathologic neovascular (NV) areas at P17 to assess the effects of1 Hmox1 competitive inhibition, and2Hmox1 allosteric inhibition.
Results: Iron trafficking genes across different retinal cell-types were upregulated in OIR, including CP, FTH1, IREB2, TF, and Hmox1. Moreover, Prussian blue staining suggests iron accumulation in retinal vessels exposed to OIR. Hmox1 mRNA (n=7, P<0.01 at P17) and protein expression (n=3, P<0.05) were increased 3.8-fold from P12 to 19. Immunostaining and single-cell RNAseq confirmed that Hmox1 predominantly resides in retinal microglial cells. Competitively and allosterically Hmox1 inhibition decreased NV by 15% (n=15, P=0.02) and 60% (n=5, P<0.01) respectively.
Conclusions: Iron metabolism has seldom been explored in the context of ROP. Perhaps microglial heme metabolism by Hmox1 contributes to HIF1α stabilization and pathological NV.
Keywords: Retinopathy of prematurity (ROP); iron metabolism; microglia

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