Hematological and Vascular Defects in a Model of Null and Type 2B VHL Mutations

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Von Hippel-Lindau (VHL) syndrome is an autosomal dominant predisposition to cancer in neurological tissues, the kidneys, adrenal glands, pancreas, and liver, including neurological hemangioblastoma (HB), pheochromocytoma (PCC), pancreatic neuroendocrine tumors (PNET), pancreatic and renal cysts, and clear cell renal cell carcinoma (ccRCC). The disease process aligns with Knudson's two-hit model, requiring spontaneous loss or mutation of a normal VHL tumor suppressor allele to induce manifestation of the disease. VHL syndrome principally involves dysregulation of oxygen sensing pathways including the Hypoxia Inducible Factor (HIF)-Vascular Endothelial Growth Factor-A (VEGF-A) and HIF-Erythropoietin (EPO) signaling axes. RNA sequencing (RNA-Seq) data from our previous work in the developing retina (Arreola et al. JCI Insight 2018) revealed that induced null and Type 2B VHL mutations yielded elevated VEGF-A expression, with the existence of a potentially novel VEGF-A splice variant lacking the VEGF Receptor-1 (VEGFR-1)/Flt-1 binding domain, which would render this isoform resistant to native down-regulation. Extending this early postnatal model (postnatal day 7-21, P7-21) to juvenile/young adult stages (P43-60), consistent phenotypic changes were observed in VHL mutant mice, specifically very red appearing extremities and ears with prominently visible vasculature. In order to determine the etiology of this phenotype, we measured red blood cell count, *Epo* gene expression levels, and arterialization of the blood vessels in these experimental mice as compared to littermate controls. Research is ongoing to conclusively identify the presumptive VEGF-A isoform, though we observed an associated decrease in retinal expression of Claudin-5, a tight junction molecule critical for vessel barrier function. Preliminary data further indicates a multifactorial and age-dependent etiology for the erythematous phenotype downstream of VHL mutations, with future studies aimed at establishing the molecular mechanisms underlying the hematological and vascular changes observed.