Genetics Day Poster Submission

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Title: THE ROLE OF PLATELET DERIVED GROWTH FACTOR RECEPTOR AND ARYL-HYDROCARBON RECEPTOR SIGNALING IN TED PATHOGENESIS

Abstract: Autoimmune thyroid diseases, including Graves' disease, affect up to 5% of the global population. Up to half of these patients may develop thyroid eye disease (TED), a debilitating condition that can lead to ocular irritation, bulging eyes (proptosis), optic neuropathy and vision loss. In TED, the connective tissue behind the eye becomes inflamed, enlarged, and remodeled. TED has perplexed scientists for decades and remains an uncurable disease. Additionally, no animal models have been able to faithfully reproduce orbital disease. Risk factors for TED include: age, microvascular disease, and tobacco use. Orbital fibroblasts are central mediators of TED as they proliferate excessively, produce high levels of extracellular matrix (ECM) and inflammatory cytokines. TED orbital tissue contains high levels of platelet-derived growth factors (PDGF). Orbital fibroblasts express PDGF receptors (PDGFRs) and proliferate rapidly and produce high levels of extracellular matrix when exposed to PDGF. The aryl hydrocarbon receptor (AHR) is a ligand activated transcription factor also expressed by orbital fibroblasts. The AHR is most well-known for its ability to respond to environmental toxins including components of cigarette smoke and dioxin, however AHR also binds to short-lived, endogenously produced tryptophan derivatives. Activation of the AHR by these short-lived endogenous ligands serves to block fibroblast growth and activation. The objective of this research is to investigate the ability of AHR to limit PDGF signaling in TED. Here, orbital fibroblasts from TED patients were cultured and treated with PDGF in the presence or absence of the tryptophan derivative and AHR ligand, FICZ. Cells were collected and analyzed by Western blot and qPCR for proliferation markers, signaling proteins and AHR target gene expression. Functional assays measuring cell migration were also used. Activation of orbital fibroblasts with PDGF led to a robust increase in AKT phosphorylation and expression of thymidylate synthase, an enzyme involved in DNA precursor synthesis and cell proliferation. Activation of the AHR by FICZ inhibited PDGF signaling. PDGF signaling also increased orbital fibroblast proliferation and migration while FICZ mitigated this effect. AHR knockdown experiments revealed that AHR expression was required to block PDGFR signaling. These preliminary data show that activation of the AHR by FICZ inhibits PDGF signaling in orbital fibroblasts and reveal that AHR activation may be a novel mechanism to treat TED.