AUTHORS

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Study Group:

ABSTRACT

TITLE: Investigating the role of peroxisome proliferator-activated receptor-β/δ (PPARβ/δ) in wet age-related macular degeneration (AMD)

ABSTRACT BODY:

Purpose: The majority of AMD-related severe vision loss occurs in patients with the wet form of the disease. It is characterized by pathological neovascularization from the choriocapillaris. Given only a fraction of AMD patients demonstrate benefit with the current anti-VEGF therapies, it is crucial to identify other pathogenic mechanisms involved in neovascularization. PPARs are members of a family of lipid activated nuclear receptors. Since the PPARβ/δ isoform has been shown to regulate angiogenesis and inflammation, we investigated its role in wet AMD.

Methods: Cell migration and tube formation in RF/6A (macaque choroidal endothelial) cells were analyzed after PPARβ/δ knockdown, ligand (agonist or antagonist) treatment, and incubation with conditioned media (CM) from ARPE19 (human retinal pigment epithelium) cells treated with PPARβ/δ ligands. The choroid was examined in eyes from aged Pparβ/δ−/− and Pparβ/δ+/+ mice by electron microscopy. The effect of PPARβ/δ expression (Pparβ/δ−/+ and Pparβ/δ−−) and pharmacological modulation [vehicle control, PPARβ/δ antagonist (GSK0660) or PPARβ/δ agonist (GW0742)] on choroidal neovascular (CNV) lesion severity was examined in isolectin-IB4 stained flatmounts of mouse eyes following laser induced CNV. Cryosections from Pparβ/δ−/− and Pparβ/δ+/+ eyes were probed with antibodies to Iba1 and F4/80, to evaluate microglial localization within the CNV lesions.

Results: Knocking down PPARβ/δ expression with siRNA or antagonizing PPARβ/δ function decreased bFGF-induced cell migration and tube formation. Additionally, treatment of ARPE19 CM with a PPARβ/δ antagonist was able to reverse CM-induced migration of RF/6A cells. While ultrastructural images displayed no differences in the choroid between Pparβ/δ−/− and Pparβ/δ+/+ controls, Pparβ/δ−/− mice exhibited decreased volume and size of CNV lesions and a 2-fold higher localization of Iba1+ and F4/80+ microglia as compared to age-matched controls.

Conclusions: These results support our previous findings that PPARβ/δ regulates AMD pathobiology in a cell-specific manner. While PPARβ/δ antagonism may have therapeutic benefit in the context of the choroid and wet-AMD, RPE cells might benefit from ligand activation of PPARβ/δ to treat sub-RPE deposit formation. Finally, the increase in microglial cells within smaller CNV lesions may be indicative of macrophage polarization regulated by PPARβ/δ.

Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand.

Describe the big picture and the implications of your findings, not the study itself and the associated details.: Age-related macular degeneration is an eye condition, which leads to progressive vision loss in the elderly, affecting approximately 15 million Americans and many more Worldwide. This disease damages the sharp central vision compromising the ability of the person affected to perform daily tasks such as driving, reading, and recognizing faces. During the later stages, the disease can progress to “wet” or neovascular AMD. There are treatments offered to patients with “wet” AMD, which are effective to varying degrees, but only in about 30-60% of patients. This leaves approximately 30% of the patient population for which an alternative treatment must be found. Our study aims to test a
different class of drugs for the treatment of “wet” AMD that target a novel pathway in the development of the disease. This pathway has been shown to be an important target in the treatment of atherosclerosis and diabetes, diseases which share a few common characteristics with AMD. We hope that our research will lead to development of an alternative treatment for the management of wet-AMD.

DETAILS

PRESENTATION TYPE: #1 Paper, #2 Poster
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Registration Number (Abstract):
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TRAVEL GRANTS and AWARDS APPLICATIONS

AWARDS: ARVO and ARVO Foundation Travel Grants|ARVO Members-in-Training Outstanding Poster Award