Loss of Apolipoprotein E Results in Altered Aqueous Humor Lipidome and Reduced ERG Response in Mice

Anoop Magesh[1], Reshma Magesh[1], Sutha K. John[3], Jungsu Kim[2, 3], Padmanabhan P. Pattabiraman[1, 3]

1. Ophthalmology, Indiana University School of Medicine, Indianapolis, IN, United States.
2. Medical & Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN, United States.
3. Stark Neuroscience Research Institute, Indiana University School of Medicine, Indianapolis, IN, United States

Purpose

Elevated intraocular pressure (IOP) is a risk factor for primary open-angle glaucoma (POAG). Apolipoprotein E (APOE) is a cholesterol transport protein implicated with POAG risk. Preliminary data from the lab has shown that loss of APOE *in-vivo* have resulted in IOP elevation in mice. In this study, we aimed to elucidate APOE's role in IOP homeostasis and POAG pathology via lipid-mediated pathways and analyses.

Methods

Wild-type (WT) and *ApoE*^{tm1Unc} knock-out homozygous (*ApoE*$^{-/-}$) mice were used for this study. We performed: aqueous humor (AH) tap (13 mice) and shotgun lipidomics; pathway analyses using MetaboAnalyst 5.0; histology (6 mice) to validate knockout; electroretinogram (ERG) at three flicker intensities (-20, -10, 0 dB), comparing amplitudes of a and b-waves between WT and ApoE-/- mice using LKC Software EMWin 8.1 (n=4). Significance was conducted using Student's t-test for significance ($p<=0.05$) using GraphPad Prism 9.0.

Results

AH lipidomics showed significant lipid changes in *ApoE*$^{-/-}$ mice: elevated cholesteryl esters, ceramides, phosphoglycerides, and triglycerides, and decreased sphingomyelins and free fatty acids. Metabolic pathway analysis showed notable changes in mitochondrial β-oxidation and arachidonic acid metabolism pathways. ERG analysis showed reduced amplitude in *ApoE*$^{-/-}$ mice for both a-wave and b-waves at all intensities.

Conclusions

Our study indicates APOE plays a significant role in the aqueous humor lipidome in mice. Reduced ERG response patterns in *ApoE*$^{-/-}$ mice suggest a phenotypical insult to retinal subcomponents, possibly worsened by prolonged ocular hypertension. Monitoring ERG response progression with IOP changes in mice will help elucidate APOE's effects through future investigation. Additionally, the observed extracellular ceramide elevation in AH may contribute to age-related pathologies, warranting further investigation in TM outflow pathophysiology. Ongoing and future studies will aim to delineate the metabolic and physiological effects of APOE knockout in human TM tissue culture.

Funding Source

NIH/NEI -R01EY029320 and R01EY035412, Ralph W. and Grace M. Showalter Research Trust and the Indiana University School of Medicine, Research Support Funds Grant (RSFG), Challenge Grant from Research to Prevent Blindness (RPB) to IU, and RPB Pilot Grant.