**Autophagy in Neurodegeneration and Neuroinflammation in Glaucoma**

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**INTRODUCTION**

This pilot project aimed for improved molecular understanding of autophagy regulation in glaucoma.

We hypothesize based on accumulating evidence that the molecular regulation and outcomes of autophagy during glaucomatous neurodegeneration are key factors in the disease, which we aim to study in mouse models and in human samples. Our hypothesis is based on the observation that autophagy is critical in the survival of retinal ganglion cells (RGCs) and that its dysfunction can lead to neurodegeneration and optic nerve damage.

**RESULTS**

**For setting a baseline for our proposed molecular analysis in transgenic mouse models, we first analyzed the cellular outcomes of ocular hypertension in mice and characterized the cell type-specific molecular responses to experimental mouse glaucoma.** While we are progressing towards the generation and cell type-specific analysis of Rab7 and mTOR, our initial studies have focused on the outcomes of astroglial IκKα deletion.

**CONCLUSIONS**

**These findings further support the role for astroglial NF-κB in cell type-specific regulation of autophagy in mouse glaucoma.** Predominant activation of NF-κB in glaucomatous astroglia might repress autophagy through the activation of autophagy inhibitor, mTOR (also supported by our previous observations). This likely reflects an autoregulatory feedback loop to control cell survival versus cellular death. NF-κB activation is also followed by activation of inflammatory cytokines (such as TNF-α and IFN-γ). Given the complex regulation of glaucomatous neurodegeneration that involves multiple sites of injury, diverse cell types, and multiple pathways, new treatment strategies are likely to be multi-targeted and effective.

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**DESIGN & METHODS**

Our ongoing work pursues two opposing experimental paradigms of decreased autophagic flux (by deletion of Rab7, which promotes the fusion of autophagosomes with lysosomes, or endosomes), and increased autophagic flux (by deletion of mTOR, which is an upstream negative regulator). Related transgenic lines are generated by breeding the specific cell types (e.g., Thy-1.2+ or (GFAP/cre/ERT2) for RGC- or astroglia-specific conditional deletion, respectively. Additional lines, similarly generated by the cre-lox system, include GFAP/cre/ERT2 to also study the role of glial cells in the regulation of inflammation (specifically in neuroinflammation in glaucoma) in molecular regulation of autophagy in astrocytes.

**NEXT STEPS**

To speed the scientific understanding of molecular processes towards new treatment paradigms for glaucoma patients, cell type-specific analysis is essential. We continue to systematically analyze the temporal course of cell type-specific responses to cell type-targeted transgenic deletion of specific molecules in retina and optic nerve head (head) of mouse eyes with or without induced ocular hypertension.

Ongoing studies are expected to further characterize cell type-specific, site-specific, and temporospatial outcome of glaucoma in the development of new treatment strategies for immunomodulatory and neuroprotective treatments in glaucoma.