PZ2 Gene is a Potential Target for Glaucoma Treatment

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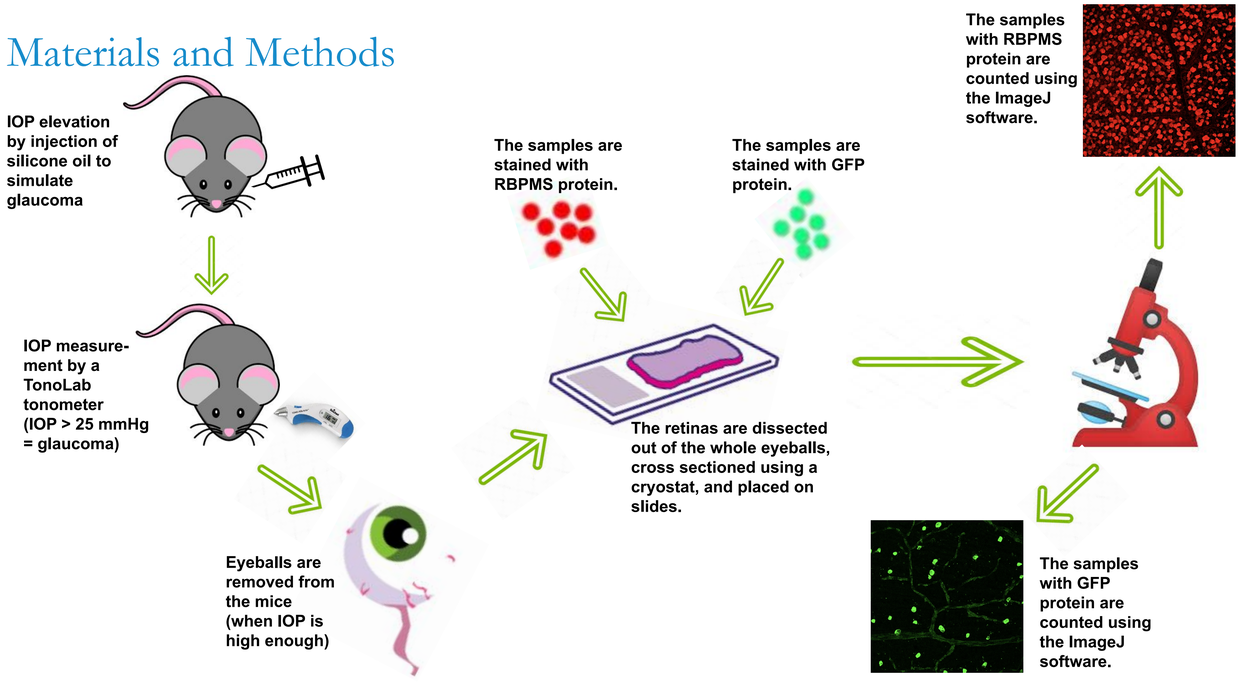
Abstract

Glaucoma is a neurodegenerative disease characterized by the injury to the axons of retinal ganglion cells, most commonly caused by elevated intraocular pressure. Current treatments for glaucoma include prostaglandin derivatives, beta-blockers, carbonic anhydrase inhibitors, and alpha-adrenergic agonists, but all these treatments either are extremely costly or have severe side effects. However, another potential approach to treat glaucoma could have a genetic foundation. By identifying particular genes that influence the resistance of retinal ganglion cells to cell death as a result of elevated intraocular pressure, potential treatments for glaucoma could be developed to be not only be more effective with lesser side effects, but also assist scientists in gaining a better longitudinal understanding of the molecular mechanisms of glaucomatous degeneration. This project utilizes these potential benefits of a genetic approach to glaucoma treatment as a basis to identify which gene, either the KCNG gene or the PZ2 gene, has a higher survival rate under glaucoma conditions. Silicone-oil injections stimulate glaucoma conditions in the mouse eye for both the KCNG and the PZ2 genes, and the resulting retinal samples, stained with the GFP and RBPMS proteins, were used to count the surviving retinal ganglion cells. Ultimately, we identified the PZ2 gene as a potential target for glaucoma treatment as it had a higher survival rate of retinal ganglion cells.

Objective

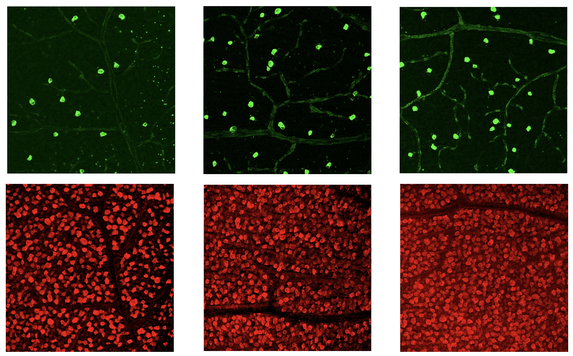
Glaucoma is the most common cause of irreversible blindness and is a neurodegenerative disease characterized by injury to the axons of different subsets of retinal ganglion cells (RGCs), most commonly caused by elevated intraocular pressure. The purpose of this project is to identify which gene results in RCGs that are most resistant to cell death by glaucoma in order to provide information that could lead to the development of targeted therapies for glaucoma. To do this, the mouse animal model was used to simulate glaucoma conditions through elevated IOP by using the silicone-oil ocular hypertension/glaucoma model (SOHU). Previous research has identified the KCNG and PZ2 genotypes in the retinas of mice to be favorable for replicating glaucoma. The goal of our project is to identify which subset of RCGs, either the KCNG gene or the PZ2 gene, presents with least cell death under glaucoma conditions in mouse retinas. Ultimately, we hope that our research will contribute to a better longitudinal assessment of the molecular mechanisms of glaucomatous degeneration and help maximize the efficacy of neuroprotectants in the future.

Materials and Methods



Results

PZ2 Samples



1A) Stained with GFP

Figure 1A: Cross sections of retinas produce images of RGCs that were stained with the GFP protein to display the larger retinal cells. **Average cells stained with GFP from all KCNG samples: ~20**

1B) Stained with RBPMS

Figure 1B: Cross sections of retinas produce images of RGCs that were stained with the RBPMS protein to display the smaller retinal cells. **Average cells stained with RBPMS from all KCNG samples: ~542**

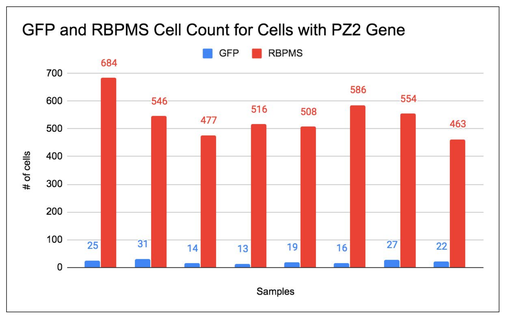
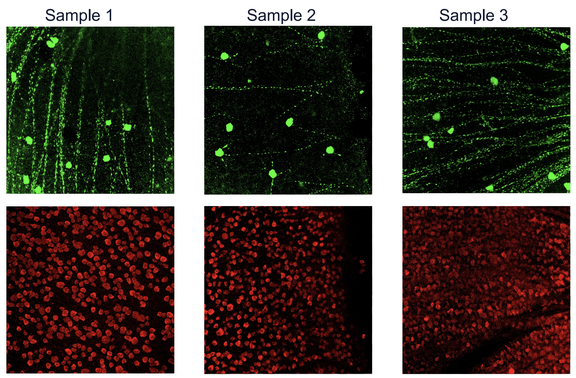


Figure 3: Total cell counts of all retinal samples with the PZ2 gene. After staining and taking cross sections of all the samples, the cells in each sample were counted with a software known as ImageJ.

KCNG Samples



2A) Stained with GFP

Figure 2A: Cross sections of retinas produce images of RGCs that were stained with the GFP protein to display the larger retinal cells. **Average cells stained with GFP from all KCNG samples: ~11**

2B) Stained with RBPMS

Figure 2B: Cross sections of retinas produce images of RGCs that were stained with the RBPMS protein to display the smaller retinal cells. **Average cells stained with RBPMS from all KCNG samples: ~367**

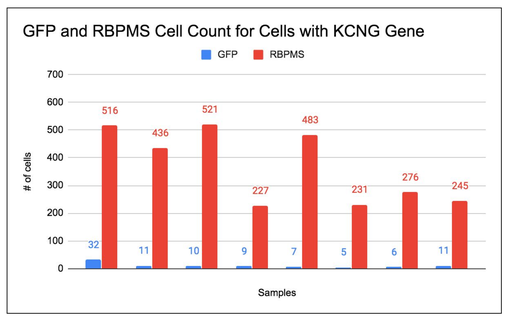


Figure 4: Total cell counts of all retinal samples with the KCNG gene. After staining and taking cross sections of all the samples, the cells in each sample were counted with a software known as ImageJ.

Relevance to Biotechnology

In this study, we successfully identified the PZ2 gene as the gene that yields stronger RGCS with a lower overall cell death under glaucoma conditions when compared with the KCNG gene. This advancement is crucial in helping scientists understand which genes to target specifically when developing neuroprotectants and other treatments for glaucoma. Any future treatments with a genetic foundation could have extremely far reaching effects globally because glaucoma is the most common cause of irreversible blindness, and it is imperative to develop a more efficient and successful treatment for this disease.

Conclusions

Glaucoma is a neurodegenerative disease characterized by injury to the axons of different subsets of RGCs. The most common risk factor for glaucoma is an elevated IOP. To overcome this problem, researchers have developed several treatments to lower IOP, including prostaglandin derivatives, beta-blockers, carbonic anhydrase inhibitors, and alpha-adrenergic agonists, However, these treatments are costly and have many deleterious side effects. In one study, JV et al. found that argon laser trabeculoplasty (ALT) greatly reduced IOP in patients with glaucoma. However, ALT has several harmful side effects: first, the surgery is an invasive process; second, the major consequence noted was a rise in IOP, with other complications including 3% of eyes worsening after ALT treatment as well as a total loss of vision due to elevated IOP in one case; third, such treatment methods are costly. Current clinical therapies target reduction of IOP to retard glaucomatous neurodegeneration, but neuroprotectants are critically needed to prevent degeneration of RGCs and ON. Thus, By targeting a specific gene directly, we could potentially avoid some of the side effects of existing treatments. Furthermore, while other treatments have a much broader scope, treatments targeting specific genes will effectively lower the cell death caused by glaucoma. Eventually, we hope that our identification of the potential target gene of PZ2 will contribute to a better longitudinal understanding of the molecular mechanisms of glaucomatous degeneration, fueling the continuation of developing better treatments for this condition.

Acknowledgments:

I would like to thank my parents for all their help and support throughout the course of my research as well as Dr. Xin Duan, Dr. Victoria Zhao, and other members of the Duan Lab who graciously provided me with guidance and gave me the opportunity to carry out this research in the first place.