Optic Nerve Relays for the Restoration of Visual Function

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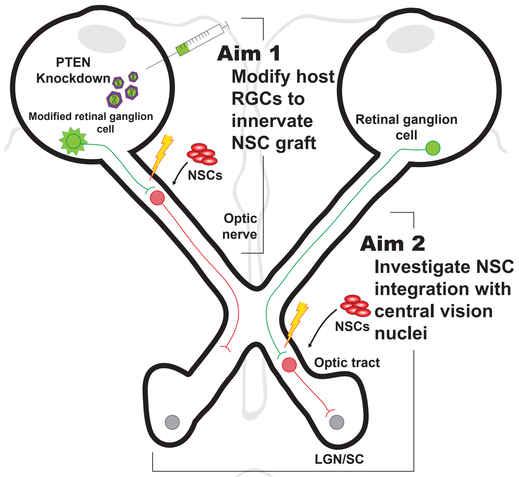
INTRODUCTION

- Axonal connections between the retina and vision centers in the brain must be reconstructed to restore vision.
- Retinal ganglion cell (RGC) axons do not spontaneously regenerate following injury.
- Neural stem cells (NSCs) transplanted into optic nerve have the potential to reconstruct damaged connections between RGC axons and neuronal targets.

Project Aims

- Modify RGCs to enhance innervation of optic nerve transplanted NSCs
- Evaluate the extent to which NSCs in the visual pathway integrate with central vision nuclei

DESIGN & METHODS



Aim 1: Modify host RGCs to innervate grafted NSCs

- Enhance host RGC axon regeneration using adeno-associated virus (AAV)-mediated knockdown of PTEN
- Evaluate modified host RGC axon innervation of optic nerve transplanted NSCs

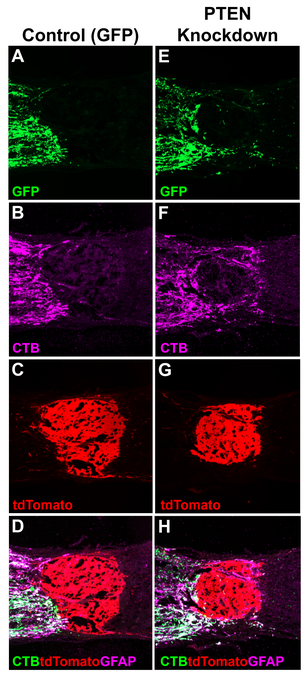
Aim 2: Investigate NSC integration with central vision-associated nuclei

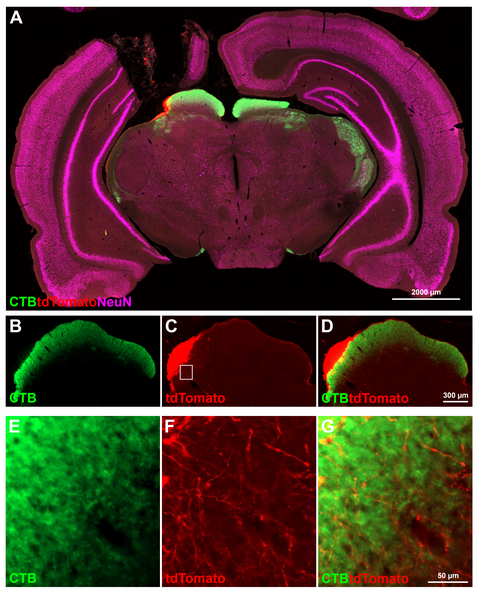
- Facilitate NSC integration into the visual system by transplanting NSCs into the optic tract
- Analyze degree of NSC connectivity with central vision-associated nuceli

RESULTS

PTEN Knockdown in Host RGCs Enhances RGC Axon Regeneration into Optic Nerve Grafted NSCs

- Intravitreally injected AAV transduced host RGCs to express a green fluorescent protein (GFP) reporter **(A)** or short hairpin RNA targeting PTEN expression and GFP **(E)**
- PTEN knockdown promoted the regeneration of RGC axons labelled with cholera toxin B subunit (CTB) **(B and F)**
- More RGC axons regenerated into tdTomato-expressing NSCs grafted into the optic nerve **(C and G)** and when RGC PTEN expression was downregulated **(D and H)**





Transplanted NSCs Extend Axons into the Superior Colliculus to Integrate with the Host Visual Pathway

- NSCs expressing tdTomato survived transplantation into the optic tract **(A)**
- Optic tract grafted NSC axons innervated the host superior colliculus labelled with CTB **(B-D)**
- NSC graft-derived axon terminals demonstrated end bulb-like morphologies within the superior colliculus **(E-G)**

CONCLUSIONS

- RGCs modified through the disruption of PTEN expression regenerate a greater number of axons that innervate NSCs grafted into the optic nerve
- NSCs grafted into the optic tract extend axons that have the capacity to innervate visual centers in the brain
- RGC modifications in combination with NSCs transplanted within the visual pathway have the potential to reconstruct retinofugal connections and restore vision

NEXT STEPS

- Target complementary RGC pathways that further enhance RGC survival and axon regeneration to facilitate the formation of RGC-NSC connections
- Evaluate NSCs transplanted into the visual pathway for functional synapses, axon myelination, electrophysiological activity, and vision-related behavioral outcomes
- Modify NSCs to enhance the integrative capacity of the grafted cells when transplanted into the optic nerve by augmenting cell survival, axon extension, axonal guidance, and synapse formation

ACKNOWLEDGEMENT

This study was supported in part by the **Glaucoma Research Foundation**, San Francisco, CA. In addition, Dr. Do is supported by a K08 Career Development Award from the National Eye Institute and the Department of Ophthalmology at the University of California San Diego is supported by an unrestricted grant from Research to Prevent Blindness.