

# *The Neuroscience Graduate Program*

*presents:*

**STEPHANIE SYC-MAZUREK**

**ADVISOR: RICHARD LIBBY**

*IN A PHD THESIS DEFENSE*

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***The molecular signaling pathways controlling apoptotic retinal ganglion cell death after axonal injury***

Vision loss in glaucoma is characterized by the stereotypical death of retinal ganglion cells (RGCs). Ocular hypertension is a major risk factor for glaucoma and is thought to trigger glaucomatous neurodegeneration through injury to RGC axons. The cellular signaling pathway leading from ocular hypertension to RGC degeneration, however, is not well defined. Understanding the molecular pathways that contribute to glaucomatous neurodegeneration will inform the rational design of new pharmacologic interventions. The focus of these studies was to identify the molecular signaling pathway(s) critical for RGC death in glaucoma. JNK-JUN signaling, a component of the mitogen-activated protein kinase (MAPK) family, is a regulator of neurodegeneration in many different systems. After mechanical axon injury, an injury thought to mimic glaucomatous damage to RGC axons, JNK-JUN signaling has been shown to be important in RGC death. To determine if JNK-JUN signaling is active in RGCs after an ocular hypertensive insult, the expression of JUN and JNK were tested in the DBA/2J mouse, a mouse model of ocular hypertension. JUN and JNK were found to be activated in a temporal and spatial pattern consistent with regulating glaucomatous neurodegeneration. To assess the importance of this pathway after an ocular hypertensive injury, optic nerves from *Jun* deficient and wild type aged DBA/2J mice were scored for optic nerve damage. No difference was observed in the severity of optic nerve damage between genotypes, with both groups having significant axonal degeneration. *Jun* deficiency did significantly protect RGC bodies (somas) as compared to control eyes. Despite the protection to RGC somas conferred by *Jun* deficiency after ocular hypertensive injury, *Jun* deficiency did not provide complete protection to RGC somas. Furthermore, after mechanical optic nerve crush *Jun* deficiency did not protect all RGCs at extended time points after injury. Together these data suggest another pro-death signaling pathway is critical for RGC somal degeneration after axonal injury. Another major regulator of axon injury induced RGC death is endoplasmic reticulum (ER) stress, specifically its target gene, *Ddit3*. JUN and DDIT3 expression were found to be independently regulated in RGCs after axonal injury, suggesting each can independently control axonal injury induced RGC death. To test the possibility that JUN and DDIT3 together control RGC fate after injury, *Jun* and *Ddit3* deficient mice were generated and subjected to optic nerve injury. Inhibiting these two pathways together appears to have an additive effect on RGC survival, providing profound/near complete protection even at extended time points after optic nerve crush. These results suggest JUN and DDIT3 are independently regulated pro-death signaling molecules in RGCs and together control apoptotic signaling in RGCs after axonal injury. Preventing glaucomatous neurodegeneration will likely require the inhibition of several pro-death signaling pathways as both MAPK and ER stress signaling are important for RGC death after axonal injury.