

Soluble Tumor Necrosis Factor Alpha Promotes Retinal Ganglion Cell Death in Glaucoma via Calcium-Permeable AMPA Receptor Activation

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Loss of vision in glaucoma results from the selective death of retinal ganglion cells (RGCs) . Tumor necrosis factor α (TNF α) signaling has been linked to RGC damage, however, the mechanism by which TNF α promotes neuronal death remains poorly defined. Using an in vivo rat glaucoma model, we show that TNF α is upregulated by Müller cells and microglia/macrophages soon after induction of ocular hypertension. Administration of XPro1595, a selective inhibitor of soluble TNF α , effectively protects RGC soma and axons. Using cobalt permeability assays, we further demonstrate that endogenous soluble TNF α triggers the upregulation of Ca²⁺-permeable AMPA receptor (CP-AMPA) expression in RGCs of glaucomatous eyes. CP-AMPA activation is not caused by defects in GluA2 subunit mRNA editing, but rather reflects selective downregulation of GluA2 in neurons exposed to elevated eye pressure. Intraocular administration of selective CP-AMPA blockers promotes robust RGC survival supporting a critical role for non-NMDA glutamate receptors in neuronal death. Our study identifies glia-derived soluble TNF α as a major inducer of RGC death through activation of CP-AMPARs, thereby establishing a novel link between neuroinflammation and cell loss in glaucoma.

SIGNIFICANCE STATEMENT: Tumor necrosis factor α (TNF α) has been implicated in retinal ganglion cell (RGC) death, but how TNF α exerts this effect is poorly understood. We report that ocular hypertension, a major risk factor in glaucoma, upregulates TNF α production by Müller cells and microglia. Inhibition of soluble TNF α using a dominant-negative strategy effectively promotes RGC survival. We find that TNF α stimulates the expression of calcium-permeable AMPA receptors (CP-AMPA) in RGCs, a response that does not depend on abnormal GluA2 mRNA editing but on selective downregulation of the GluA2 subunit by these neurons. Consistent with this, CP-AMPA blockers promote robust RGC survival supporting a critical role for non-NMDA glutamate receptors in glaucomatous damage. This study identifies a novel mechanism by which glia-derived soluble TNF α modulates neuronal death in glaucoma.

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