*During Glaucoma, α2-Macroglobulin Accumulates in Aqueous Humor and Binds to Nerve Growth Factor, Neutralizing Neuroprotection*

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**PURPOSE:** Glaucoma is an optic neuropathy caused by the chronic and progressive death of retinal ganglion cells (RGCs), resulting in irreversible blindness. Ocular hypertension is a major risk factor, but RGC death often continues after ocular hypertension is normalized, and can take place with normal tension. Continuous RGC death was related in rodents and humans to the local upregulation of neurotoxic proteins, such as TNF-α. In rat models of glaucoma, ocular hypertension also upregulates the expression of α2-macroglobulin, which is neurotoxic. α2-macroglobulin upregulation in the retina is long-lived, even after high IOP is reduced with medication. α2-macroglobulin is examined as a possible biomarker in human glaucoma, and a possible neurotoxic mechanism of action is sought.

**METHODS:** Quantitative Western blotting of α2-macroglobulin in samples obtained from aqueous humor (human and rat) and retina (rat) was conducted. Ex vivo neuronal survival assays and nerve growth factor-α2-macroglobulin binding studies using surface plasmon resonance were used.

**RESULTS:** Increased soluble α2-macroglobulin protein is also present in the aqueous humor in a rat glaucoma model, as well as in the aqueous humor of human glaucoma patients but not in cataract patients. One mechanism by which α2-macroglobulin is neurotoxic is by inhibiting the neuroprotective activity of nerve growth factor via TrkA receptors.

**CONCLUSIONS:** This work further documents a potential novel mechanism of RGC death and a potential biomarker or therapeutic target for glaucoma.
