Complement C3-Targeted Gene Therapy Restricts Onset and Progression of Neurodegeneration in Chronic Mouse Glaucoma

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Dysregulation of the complement system is implicated in neurodegeneration, including human and animal glaucoma. Optic nerve and retinal damage in glaucoma is preceded by local complement upregulation and activation, but whether targeting this early innate immune response could have therapeutic benefit remains undefined. Because complement signals through three pathways that intersect at complement C3 activation, here we targeted this step to restore complement balance in the glaucomatous retina and to determine its contribution to degeneration onset and/or progression. To achieve this, we combined adeno-associated virus retinal gene therapy with the targeted C3 inhibitor CR2-Crry.

We show that intravitreal injection of AAV2.CR2-Crry produced sustained Crry overexpression in the retina and reduced deposition of the activation product complement C3d on retinal ganglion cells and the inner retina of DBA/2J mice. This resulted in neuroprotection of retinal ganglion cell axons and somata despite continued intraocular pressure elevation, suggesting a direct restriction of neurodegeneration onset and progression and significant delay to terminal disease stages.

Our study uncovers a damaging effect of complement C3 or downstream complement activation in glaucoma, and it establishes AAV2.CR2-Crry as a viable therapeutic strategy to target pathogenic C3-mediated complement activation in the glaucomatous retina.

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