

Cumulative mtDNA damage and mutations contribute to the progressive loss of RGCs in a rat model of glaucoma

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Glaucoma is a chronic neurodegenerative disease characterized by the progressive loss of retinal ganglion cells (RGCs) . Mitochondrial DNA (mtDNA) alterations have been documented as a key component of many neurodegenerative disorders. However, whether mtDNA alterations contribute to the progressive loss of RGCs and the mechanism whereby this phenomenon could occur are poorly understood. We investigated mtDNA alterations in RGCs using a rat model of chronic intraocular hypertension and explored the mechanisms underlying progressive RGC loss.

We demonstrate that the mtDNA damage and mutations triggered by intraocular pressure (IOP) elevation are initiating, crucial events in a cascade leading to progressive RGC loss. Damage to and mutation of mtDNA, mitochondrial dysfunction, reduced levels of mtDNA repair/replication enzymes, and elevated reactive oxygen species form a positive feedback loop that produces irreversible mtDNA damage and mutation and contributes to progressive RGC loss, which occurs even after a return to normal IOP.

Furthermore, we demonstrate that mtDNA damage and mutations increase the vulnerability of RGCs to elevated IOP and glutamate levels, which are among the most common glaucoma insults. This study suggests that therapeutic approaches that target mtDNA maintenance and repair and that promote energy production may prevent the progressive death of RGCs.

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