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

Wu J1, Zhang S1, Nickerson JM2, Gao F3, Sun Z4, Chen X3, Zhang S3, Zhang R3, Gao F3, Chen J3, Luo Y3, Wang Y3, Sun X5

1 Eye & ENT Hospital, State Key Laboratory of Medical Neurobiology, Institutes of Brain Science, Shanghai Medical College, Fudan University, Shanghai 200032, China; Shanghai Key Laboratory of Visual Impairment and Restoration, Shanghai 200032, China.
2 Ophthalmology Department, Emory University, Atlanta, GA, 30322, USA.
3 Eye & ENT Hospital, State Key Laboratory of Medical Neurobiology, Institutes of Brain Science, Shanghai Medical College, Fudan University, Shanghai 200032, China.
4 Wesleyan University, Middletown, CT, 06459, USA.
5 Eye & ENT Hospital, State Key Laboratory of Medical Neurobiology, Institutes of Brain Science, Shanghai Medical College, Fudan University, Shanghai 200032, China; Shanghai Key Laboratory of Visual Impairment and Restoration, Shanghai 200032, China; Key Laboratory of Myopia, Ministry of Health, Fudan University, Shanghai 200032, China. Electronic address: xhsun@shmu.edu.cn.

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.

Copyright © 2014 Elsevier Inc. All rights reserved.


PMID: 25478814