Research Highlight

Mitochondrial Dysfunction in Glaucoma—Closing the Loop

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There is mounting evidence that glaucoma is a mitochondrial optic neuropathy, albeit a "complex" one compared to classical mitochondrial optic nerve disorders such as Leber hereditary optic neuropathy (LHON) and autosomal-dominant optic atrophy (DOA).[1] In this issue of *IOVS*, Lee et al. provide some interesting data further supporting a causal link between mitochondrial dysfunction and retinal ganglion cell (RGC) loss in primary open angle glaucoma (POAG).[2] The main finding from their study is a decreased rate of complex I-driven adenosine triphosphate (ATP) synthesis and cellular respiration in lymphoblast cell lines derived from patients with POAG. Although one should be cautious in extrapolating data from non-RGC populations, these results nevertheless are intriguing mechanistically, being entirely consistent with the predominant complex I defect previously reported for LHON and DOA.[1] Larger studies are needed to substantiate the biological trend observed between the degree of impairment in ATP synthesis and glaucoma disease severity.[2]

What disease mechanisms could account for the biochemical defect uncovered in these lymphoblast cell lines, and by extension RGCs in glaucoma? Based on preliminary data, some of which are circumstantial, there are a number of possible culprits. One possibility is the accelerated accumulation of somatic mitochondrial DNA (mtDNA) mutations—mtDNA instability being a postulated biomarker of "*normal aging*" in tissues. Another more direct mechanism is the fragmentation of the mitochondrial network and the unregulated release of pro-apoptotic cytochrome *c* molecules from the mitochondrial compartment. These pathological effects have been shown to be potentiated under conditions of raised intraocular pressure in both in vitro and in vivo models of glaucoma.[1]

For reasons that still are unclear, RGCs are exquisitely sensitive to mitochondrial dysfunction compared to other neuronal populations. Unravelling the cellular factors mediating this preferential vulnerability will be critical in identifying key disease pathways that are amenable to therapeutic manipulation.[3] Looking even more broadly, impaired mitochondrial dysfunction is an end-stage phenomenon observed in most, if not all, neurodegenerative disorders.[1] Therefore, now, more than ever, is a great opportunity for our community to invest in an area of ophthalmic research with potentially richer translational implications beyond glaucoma.

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References

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