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Protective effects of a mitochondrial-derived peptide in a macular degeneration model; implications for therapeutics

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Statement of the problem: Age-related macular degeneration (AMD), a leading retinal degenerative disease, is a primary cause of irreversible blindness among the elderly population in the United States. AMD ranks third among the global causes of visual impairment and has been listed under the category of priority eye diseases. Dry AMD which manifests as geographic atrophy affects approximately 80-90% of the patients and currently has no available treatments. Therefore, we are in need of treatment strategies for dry AMD. Mitochondrial dysfunction and the subsequent loss of retinal pigment epithelial (RPE) cells have been associated with the development and pathogenesis of AMD. Herein, we hypothesized that a mitochondrial-derived peptide called SHLP2, which is coded from the 16S rRNA gene of the mtDNA, is protective against loss of RPE in AMD cybrid cells.

Methodology & theoretical orientation: To prove our hypothesis, we used a series of cell based assays, quantitative RT-PCR, Western blotting, and immunocytochemistry. As an *in vitro* macular degeneration model, we used ARPE-19 transmitochondrial cybrid cells. All cells were treated with pre-optimized concentrations of SHLP2. Untreated cybrids served as controls.

Findings: Our results revealed that: 1) SHLP2 administration significantly improved mitochondrial function as represented by an increase in the levels of mitochondrial oxidative phosphorylation complex proteins i.e., Complex I (NADH dehydrogenase), Complex II (Succinate dehydrogenase), Complex III (CoQH2-cytochrome c reductase), Complex IV (cytochrome c oxidase), and Complex V (ATP Synthase) in AMD cybrids, and 2) Pretreatment with SHLP2 improved cell viability and preserved mitochondrial number and function in AMD cybrids.

Conclusion & significance: In conclusion, this novel study identified SHLP2 as a rescue factor that preserved cellular and mitochondrial health in an *in vitro* macular degeneration model. Our findings are significant because they demonstrated that SHLP2 could be a potential therapeutic target for the treatment of dry AMD. Further studies are needed to establish the potential of SHLP2 as a mitochondria-targeting treatment option for dry AMD.

Recent publications:

1. Sonali Nashine et al (2017). *Humanin G (HNG) protects age-related macular degeneration (AMD) transmitochondrial ARPE-19 cybrids from mitochondrial and cellular damage*. Cell Death Dis. 2017; 8(7):e2951. doi: 10.1038/cddis.2017.348.
2. Sonali Nashine et al (2016). *Differential Expression of Complement Markers in Normal and AMD Transmitochondrial Cybrids*. doi: 10.1371/journal.pone.0159828. eCollection 2016.
3. Sonali Nashine et al (2015). *Role of C/EBP homologous protein in retinal ganglion cell survival after ischemia/reperfusion injury*. Invest Ophthalmol Vis Sci.; 56(1):221-31. doi:10.1167/iovs.14-15447.
4. Choudhury S, Sonali Nashine et al (2014). *Modulation of the Rate of Retinal Degeneration in T17M RHO Mice by Reprogramming the Unfolded Protein Response*. Advances in Experimental Medicine and Biology. doi: 10.1007/978-1-4614-3209-8_58.
5. Sonali Nashine et al (2013). *Ablation of C/EBP Homologous Protein Does not protect T17M Rho mice from retinal degeneration*. PLOS ONE 8(4): e63205. doi:10.1371/journal.pone.0063205.

Biography

From the beginning of my career as an eye research scientist, my long-term research goal has been to identify therapeutic targets that rescue and/or protect retinal cells. During the course of my doctoral and postdoctoral research, I have worked on models of retinal degenerative diseases, including retinitis pigmentosa, glaucoma, and age-related macular degeneration (AMD) to identify candidate protective molecules. Currently, my research is focused on identification of potential therapeutic targets for the treatment of the dry form of age-related macular degeneration (AMD). The ideal drugs will prolong the longevity of retinal cells, delay cell death, thereby saving vision.

Notes: