Making of a mouse model:

Mitochondrial damage and clearance in retinal pigment epithelial cells in AMD

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On January 19, 2024, Iswariyaraja Sridevi Gurubaran defended his doctoral dissertation "Mitochondrial damage and clearance in retinal pigment epithelial cells: Relevance to age-related macular degeneration" for his Ph.D. at the Institute of Clinical Medicine, Faculty of Health Sciences, University of Eastern Finland. The Ph.D. project was carried out at the Dept. of Ophthalmology, University of Eastern Finland, with Prof. Kai Kaarniranta and Prof. Anu Kauppinen as co-supervisors.

Key point:

- Because aging and oxidative stress contribute to AMD, 'healthy aging' strategies, such as quitting smoking, eating healthy, and regular exercise, may help prevent disease progression.

The human sense of sight, which contributes up to 80% of environmental perception, is crucial for effective sensing, learning, and communication. Age-related macular degeneration (AMD), a major cause of visual impairment in individuals aged 60 and older, results in irreversible vision loss and blindness. AMD currently poses a substantial global socioeconomic burden of approximately USD 343 billion and is projected to affect approximately 288 million people by 2040; therefore, maintaining a properly functioning visual system is crucial to reduce the burden of AMD.

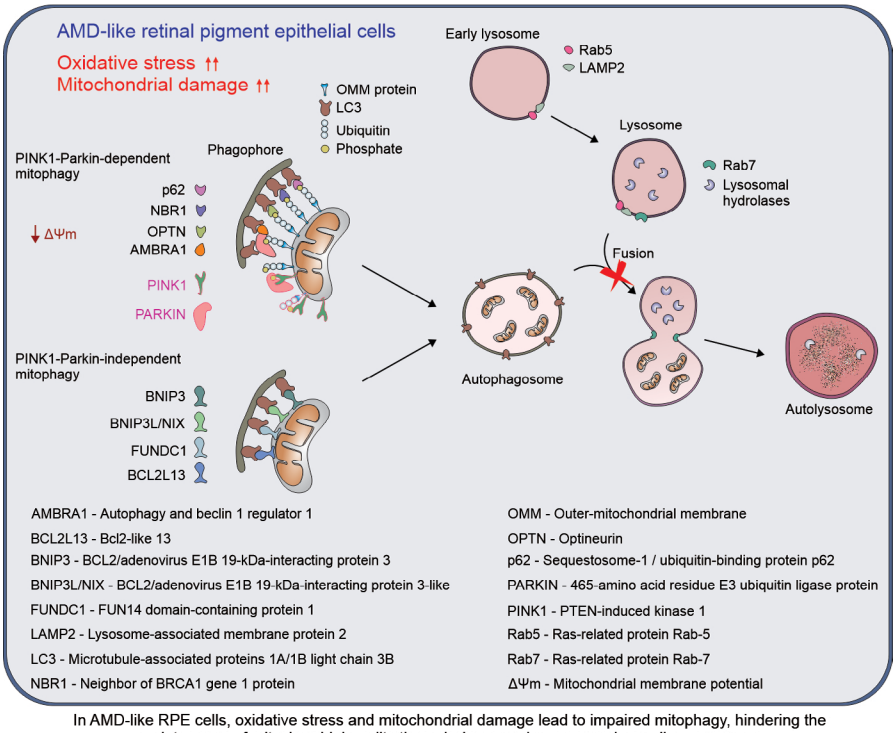
AMD arises from the degeneration of retinal pigment epithelial (RPE) cells and the subsequent loss of sensory photoreceptor cells, particularly in the macula of the retina. AMD is classified as non-exudative (dry) or exudative (wet). Dry AMD (85–95% of cases) is characterized by lysosomal lipofuscin accumulation and drusen deposits, and no treatment options are currently available. By contrast, wet AMD (10–15% of cases) involves choroidal neovascularization and is managed with intravitreal injection of anti-VEGF drugs to suppress vascular growth.

The multifactorial etiology of AMD includes genomic and epigenomic factors, environmental influences, aging, and lifestyle choices, such as smoking and a fat-rich diet. Emerging clinical evidence suggests that patients with AMD have disrupted lysosomal clearance and low-grade chronic inflammation in their RPE cells, but comprehensive research into the molecular mechanisms of these processes is needed.

To simulate aging-like oxidative stress and study AMD, we developed a mouse model with the double knockout of peroxisome proliferator-activated receptor gamma coactivator 1-alpha and nuclear factor erythroid 2-related factor 2 (PGC1α/NFE2L2). This model mimics the clinical features of dry AMD and facilitates the exploration of mitophagy—a process involving the degradation and recycling of damaged mitochondria (selective autophagy). The investigation uncovered changes in mitophagy markers, late autolysosomal fusion, Toll-like receptors, and complement components in the retina, offering insights into the potential mechanisms underlying dry AMD. The data suggest a relative decrease in mitophagy, increases in the amounts of complement component 5 and thrombin, and a decrease in complement component 3 levels in this dry AMD model.

Future directions:

- Investigations into autophagy as a potential therapeutic target for AMD



In AMD-like RPE cells, oxidative stress and mitochondrial damage lead to impaired mitophagy, hindering the maintenance of mitochondrial quality through damage clearance and recycling processes

Figure 1. The molecular mechanisms of PINK1–PARKIN-dependent and -independent mitophagy involve distinct steps. PINK1 senses the mitochondrial membrane potential (ΔΨm) and recruits PARKIN, which then phosphorylates ubiquitin and the ubiquitin-like domain of PARKIN. This activated PARKIN targets P62, NBR1, and OPTN for ubiquitination, promoting local autophagosome formation. Under stress, proteins such as BNIP3, NIX, FUNDC1, and BCL2L13 on the outer mitochondrial membrane localize there, initiating autophagosome formation. Our findings suggest that oxidative stress impedes lysosome–autophagosome fusion. Modified from Gurubaran, I.S. (2024) Mitochondrial damage and clearance in retinal pigment epithelial cells. Acta Ophthalmol, 102(Suppl. 282), 3–53. Available from: https://doi.org/10.1111/aos.16661 and (2024), Issue Information. Acta Ophthalmol, *102: 1–2. https://doi.org/10.1111/aos.16665*

References

1. Sridevi Gurubaran, I., et al. (2022). Epoxomicin, a Selective Proteasome Inhibitor, Activates AIM2 Inflammasome in Human Retinal Pigment Epithelium Cells. *Antioxidants (Basel, Switzerland)*, 11(7), 1288.
2. Sridevi Gurubaran, I., et al. (2021). Oxidative Stress and Mitochondrial Damage in Dry Age-Related Macular Degeneration Like NFE2L2/PGC-1α -/- Mouse Model Evoke Complement Component C5a Independent of C3. *Biology*, 10(7), 622.
3. Sridevi Gurubaran, I., et al. (2020). Mitophagy in the Retinal Pigment Epithelium of Dry Age-Related Macular Degeneration Investigated in the NFE2L2/PGC-1α-/- Mouse Model. *International journal of molecular sciences*, 21(6), 1976.