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A Hot Topic:

RPE cells as critical players in the retina

On September 23, 2022, Niina Harju (ex-Bhattarai) defended her thesis "Regulation of oxidative stress and inflammatory responses in human retinal pigment epithelial cells" at Faculty of Health Sciences, School of Pharmacy, University of Eastern Finland, Kuopio. The main supervisor was Anu Kauppinen, Professor, University of Eastern Finland, with co-supervisors Kai Kaarniranta, Professor, University of Eastern Finland and Kuopio University Hospital and Yashavanthi Mysore, PhD, University of Eastern Finland.

Introduction

Age-related macular degeneration (AMD) is the main cause of blindness in western countries. The prevalence of AMD is increasing, and it has been estimated to reach 288 million by 2040. There are two forms of AMD: dry (85-90% of cases) and wet (10-15% of cases). Retinal pigment epithelial (RPE) cell degeneration, eventually leading to RPE and photoreceptor cell death, occurs especially in the dry form of AMD. Typical features of the wet form are pathological neovascularization and subsequent RPE degeneration, as well as a more rapid progression of blindness. RPE cells are post-mitotic cells that appear as a single cell layer in the back of the eye, and they are important for the maintenance of the retinal homeostasis and photoreceptors functionality. During the development of AMD, protein aggregation, inflammation, NLRP3 inflammasome activation, oxidative stress, and impaired autophagy in RPE cells are all critical contributors to the disease onset (**Figure 1**). Therefore, understanding the mechanisms underlying this process is key to developing novel therapies.

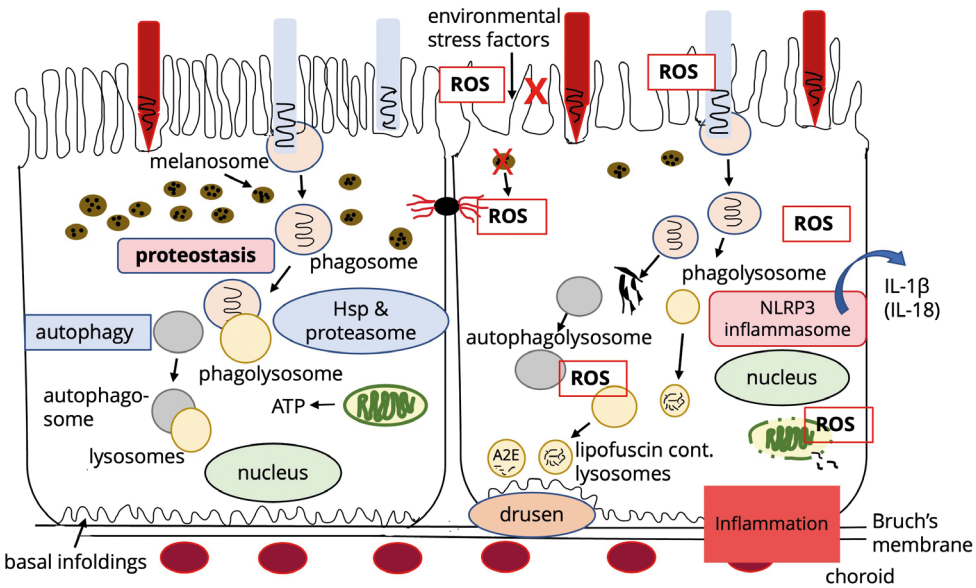

Figure 1. Comparison of a normal polarized RPE cell (left) to a dysfunctional RPE cell (right) in AMD. (Harju, N. (2022) Acta Ophthalmologica, 00, 1–58. from: https://doi.org/10.1111/aos.15275)
ROS= reactive oxygen species

Hydroquinone predisposes to the degeneration, whereas Resvega relief RPE cell responses

In my dissertation, we found hydroquinone, a component of cigarette smoke, induced NADPH oxidase-mediated ROS production and predisposed RPE cells to degeneration by reducing vascular endothelial growth factor (VEGF) level. Hydroquinone increased NLRP3-independent IL-18 release even as NLRP3 accumulated inside the IL-1α-primed RPE cells. Resvega, an antioxidant mixture including omega-3 fatty acids, vitamins C and E, copper, zinc, lutein, zeaxanthin, and resveratrol, reduced hydroquinone-induced ROS production and NLRP3 inflammasome activation induced by impaired protein clearance in RPE cells.

Key points:

- Cigarette smoke is the most important environmental risk factor for age-related macular degeneration (AMD).
- Oxidative stress, NLRP3 inflammasome activation, and inflammation contribute to AMD.
- Hydroquinone, a component of cigarette smoke, induces NADPH oxidase-mediated ROS production but reduces NF-κB activity in human retinal pigment epithelial (RPE) cells.
- Hydroquinone predisposes RPE cells to degeneration through reduced VEGF, which increases the risk of wet AMD, and is important for RPE cell viability and integrity of the retina.
- The antioxidant mixture, Resvega, reduced hydroquinone-induced oxidative stress and NLRP3 inflammasome activation induced by impaired protein clearance in RPE cells.

Looking forward

The mechanism for hydroquinone-induced cell death should be studied further as caspase-1 was not activated in degenerated RPE cells. As well, the mechanism of the IL-18 cleavage and NLRP3 inflammasome accumulation after hydroquinone exposure should be examined in more detailed. Since oxidative stress and NLRP3 inflammasome activation both contribute to the AMD, more studies are needed to figure out the potential of Resvega as a treatment option for AMD, including an optimized administration route for targeting straight to the RPE cells in the eye.

References

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