The role of smoking-induced oxidative stress and the stress receptor SUCNR1 in age-related macular degeneration

Clinical relevance

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries, affecting over 50 million individuals in the western world. AMD occurs as a wet and dry form, of which the wet form can be treated with neovascularization (VEGF-A) inhibitors. However, 80-90% of the patients suffer from dry AMD for which no treatment exists, and there a large unmet need to develop therapeutics to attenuate or cure dry AMD development. To develop such a therapy, a molecular understanding of its etiology is needed. GWAS data revealed that genes involved in inflammation and lipid handling are critically involved in AMD development and smoking worsens this. In dry AMD, insoluble extracellular lipid aggregates accumulate between the retinal pigment epithelial (RPE) layer and the underlying layer of the retina. Recently, we and others found that particular variants of the succinate receptor (SUCNR1), which is expressed in RPE cells, increase the risk of AMD development in patients.

Background

RPE cells are packed with mitochondria and are metabolically highly active, as they (1) supply photoreceptor cells (which sense light) with vitamin A, (2) recycle activated retinal to photoreceptor cells, and (3) are essential in phagocytosing membranes shed from photoreceptor cells. Upon metabolic stress, the mitochondrial metabolite succinate accumulates in the cytosol and is released from the cells, upon which it binds and activates the SUCNR1. The physiological role of the SUCNR1 in the retina and its role in AMD, however, are unknown.

Hypothesis and research questions

We hypothesize that the SUCNR1 modulates RPE lipid phagocytosis and metabolism depending on the energy balance of the RPE cells. Within the project, we aim to answer the following research questions:

- Does the SUCNR1 affect RPE lipid phagocytosis and metabolism and is this depending on its metabolic status?
- Are other AMD-related genes involved in SUCNR1-mediated phagocytosis/lipid metabolism?

What do we offer?

The possibility to perform and present high-quality clinically-oriented interdisciplinary research in a professional, multicultural and highly-motivating working team. You will work on this project under the supervision of an enthusiastic PhD student and you will have the opportunity to learn a broad range of techniques, such as fluorescent imaging, western blotting, qRT-PCR, cell culture, immunocytochemistry, microscopy, bio-informatics, planning and performing experiments and writing & presentation skills.

What will you do?

Within the project, you will be responsible for your own research project. You will set up a fluorescent lipid phagocytosis assay using an appropriate RPE cell model and study SUCNR1-mediated phagocytosis and lipid metabolism under AMD stress conditions (smoking). Released succinate levels will be determined and cells will be lysed for RNA isolation and immunoblotting. Medium of the cells will be analyzed using metabolomics. Q-RT-PCR analysis will be used to determine changes in expression of SUCNR1, (AMD-associated) genes involved in phagocytosis, lipolysis and VEGF signaling, and of other AMD-related genes. Optional is to study the circadian rhythm of pathways and AMD gene expression in RPE cells and the role of the SUCNR1 therein using bio-informatics.

Contact

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