1. The objective of the project

The retinal cells do not proliferate in normal conditions and when damaged can be replaced with cells from peripheral regions, which re-initiate the cell cycle. Disturbance of this mechanism plays an important role in the pathogenesis of retinal degenerative diseases (RDDs), which are usually age-related. Stress-induced premature senescence (SIPS), initiated by oxidative stress, induces a specific phenotype (SASP). Age-dependent degeneration of retinal pigment epithelium (RPE) cells results in accumulation of waste material, which need to be removed and recycled by autophagy. We and others have shown that impaired autophagy plays an important role in the pathogenesis of RDDs. Peroxisome proliferator-activated receptor-gamma coactivator 1α (PGC-1α) is an important component of antioxidant defense The aim of our project is to determine the role of PGC-1α in response to premature senescence induced by oxidative stress in aging RPE cells.

2. The research to be carried out

These studies will be performed on RPE cells obtained from mice at different ages with knockout in the *PGC-1a* gene and human RPE cells obtained by targeted differentiation of induced pluripotent stem (iPS) cells and *PGC-1a* silencing in these cells by the CRISPR/Cas9 technology. In our preliminary research, in which we showed an involvement of PGC-1α in the regulation of the expression of essential autophagic proteins, we confirmed the suitability of these cells for our research. Oxidative stress, senescence, autophagy and other effects will be assayed by specific markers, and microarrays. Cells will be obtained from mice at 6 and 12 months to assess the influence of aging on the studied processes. Data analysis will be performed with using of dedicated and general softwares.

3. Reasons for choosing the research topic

RDDs, including age-related macular degeneration (AMD), are featured by a massive loss of RPE cells and lack of effective treatment and they are the main reason of vision loss in the elderly in developed countries. Besides age, also oxidative stress and disturbed autophagy belong to main RDDs risk factors. Studies to determine the relationship between cellular senescence, organismal aging and autophagy could yield results important for molecular biology as there are many basic, essential and unanswered questions and problems concerning their mutual relationships. Although this proposal focuses on specific cells and tissue, its results can shed some light on fundamental problems on the cause of senescence and aging. There is an emerging scientific interest in the role of autophagy, honored last year by the Noble Prize, in the functioning of cells and organisms as this phenomenon is involved in many physiological and pathological processes including aging. However, many aspects of this involvement are not known. It is established that general autophagy and chaperon-mediated autophagy decrease with age and this effect can contribute to age-related diseases. There is no doubt that mitophagy is essential for mitochondrial aging, but the relationship between the mitochondrial and organismal aging is not clear. Moreover, general autophagy and mitophagy are important for cellular senescence, which, in turn, is important for organismal aging, but their mutual relationship is not completely clear. RDDs are a major representative of health impairment associated with age and as eye diseases, cannot be studied *in vivo* in live human retinas, so creation of a reliable *in vitro* model of these disease is required.