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Molecular and cellular mechanisms of age-related macular degeneration: evidences from OXYS rats

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Motivation and Aim: Age-related macular degeneration (AMD) is a complex neurodegenerative progressive eye disease, resulting in severe loss of central vision in the aging population. Here we present data of the analysis of clinical, histological and molecular manifestations of AMD-like retinopathy in OXYS rats, which simulate key features of AMD.
Methods: Ophthalmoscopy, analysis of RNA-Seq data, gene ontology and pathway annotation, western-blot analysis, immunohistochemistry, confocal microscopy.
Results: Using retinal mRNA profiles generated by RNA-seq we found hundreds differentially expressed (DE) genes at the preclinical (20 d), the early (3 mo) and the advanced (18 mo) stages of retinopathy in OXYS rats. Functional analysis was suggestive of a developmental process, signal transduction, and cell differentiation as the most enriched biological processes among DE genes at 20 d. Functional groups that were significantly enriched for DE genes at 3 and 18 mo included immune response, inflammation, apoptosis, Ca^{2+} homeostasis and oxidative stress. We showed that pathological processes in the retina of OXYS rats develop against the background of atrophic changes in RPE cells: the hypertrophy, the increase in variability in cell size, the increase in proportion of multinucleated cells, disruptions of the cell form, and irregular immunolabeling. The cell death in the retina of OXYS rats is realized by apoptosis, necrosis and autophagy against the background of phagocytic dysfunction and a decrease in the elimination of dead cells, as indicated by the absence of a migration of macrophages and microglia into the photoreceptor layer. The estimation of age-related alterations of autophagy process in the retina has shown the increased levels of LC3A/B, Atg7, and Atg12 proteins in the OXYS retina during manifestation stage at the age of 3 months. By contrast, in the retina of rats with a progressive stage of retinopathy, we revealed significantly decreased protein levels of autophagy markers. Simultaneously with perturbation of the autophagic response, the necrosome subunits Ripk1 and Ripk3 were detected in the OXYS retina. The downregulation of autophagy markers coincided with amyloid accumulation (Moab-2) in the retinal pigment epithelium and choroid.
Conclusion: Our study emphasizes the importance of autophagic pathway, imbalance in immune and inflammatory responses, aberrant migration of macrophages and microglia in the pathogenesis of AMD and supports the view that the genetic background has a profound impact on AMD development.
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