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Common mechanisms of Alzheimer's disease and age-related macular degeneration: focus on MAPK signaling pathways

Muraleva N.
Institute of Cytology and Genetics, SB RAS, Novosibirsk, Russia
** myraleva@bionet.nsc.ru*

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Motivation and Aim: Age is the main risk factor for Alzheimer's disease (AD) as the most common progressive senile dementia, and age-related macular degeneration (AMD), which is the leading cause of vision loss in people over 60 years of age. There are no effective ways to prevent and treat these neurodegenerative diseases, due to the incomplete knowledge of their pathogenesis. Risk factors (smoking, hypertension, hypercholesterolemia, atherosclerosis, obesity) and the mechanisms of the pathogenesis of AD and AMD are intersecting. Among them, oxidative stress, inflammation, mitochondrial dysfunctions and impaired maintenance of proteostasis with the pathological aggregation and accumulation of abnormal extracellular deposits – senile plaques in the brain of patients with AD, and in the drusen of patients with AMD. The development of these abnormalities may be associated with alteration of MAPK signaling pathways regulation with age. The contribution of impaired MAPK signalings to the pathogenesis of AD has been confirmed by the results of numerous investigations. MAPK is considered as a potential target for therapeutic interventions. Nevertheless, the information about their changes with age is limited. There are practically no data on the state of MAPK signaling activity in the retina during the development of AMD. The aim of this study was to compare changes in the activity of ERK1/2, p38MAPK and JNK signaling pathways in brain structures and retina with age and during the development of AD and AMD. We used Wistar (control) and OXYS rats as the models of accelerated aging, one of the manifestations of which is the simultaneous development of signs of AD and AMD.
Methods and Algorithms: The RNA-seq data obtained for prefrontal cortex, hippocampus and retina of Wistar and OXYS rats at the age of 20 days (signs of AMD and AD-like pathology absent), 3–5 months (period of their manifestation) and 18 months (active progression) were used to analyze differentially expressed genes involved in ERK1/2, p38MAPK and JNK signaling pathways according to Rat Genome Database.
Results: It has been established that changes in gene expression, which, according to the Rat Genome Database, are involved in p38MAPK, EPK1/2 and JNK signaling pathways, are tissue-specific and depend on the animal genotypes. In the retina, the number of differentially expressed genes (DEGs) involved in p38MAPK, ERK1/2 and JNK decreased in Wistar and OXYS rats with age. The maximum number of DEGs were detected at the age of 20 days, at the “preclinical” stage of the development of AMD-like pathology in OXYS rats. Among them were both activators and inhibitors of the activity of MAPK signaling pathways. By age three months and beyond found signs of a decrease in the activity of signaling pathways at the level of gene expression. At these

ages, only one DEG involved in the JNK signaling pathway was identified in the OXYS rat retina.

In the brain, the pattern of age-related changes in the expression profile of genes involved in ERK1/2 and p38MAPK signaling pathways in Wistar and OXYS rats was similar to that observed in the retina. In the prefrontal cortex and hippocampus, the number of DEG increased with age, the expression of which differed in OXYS compared to Wistar rats.

The level of phosphorylation of the key kinases p38MAPK, ERK1/2 and JKN signaling pathways is an objective indicator of their activity. Next, we evaluated it at the protein level by Western blot analysis. In all studied tissues – in the retina, prefrontal cortex, and hippocampus, a significant increase in the content of phosphorylated forms of p38MAPK, ERK1/2 and JNK with age was found in rats of both strains. At the same time, in OXYS rats, their accumulation was more active and increased as the signs of AD and AMD progressed.

Thus, our results showed that during physiological aging of Wistar rats and during accelerated aging of OXYS rats in the retina and brain, the direction of changes in the activity of MAPK signaling cascades both at the level of gene expression and at the protein level is the same. At the same time, it was found that the manifestation and progression of signs of AD and AMD pathology in OXYS rats occur against the background of enhanced phosphorylation of p38MAPK, ERK1/2 and JNK which makes it possible to consider an increase in the activity of MAPK signaling pathways as a common mechanism for the development of AD and AMD already at the early stages of these diseases.

Conclusion: Thus, our results showed that during physiological aging of Wistar rats and during accelerated aging of OXYS rats in the retina and brain, the direction of changes in the activity of MAPK signaling cascades both at the level of gene expression and at the protein level is the same. At the same time, it was found that the manifestation and progression of signs of AD and AMD pathology in OXYS rats occur against the background of enhanced phosphorylation of p38MAPK, ERK1/2 and JNK which makes it possible to consider an increase in the activity of MAPK signaling pathways as a common mechanism for the development of AD and AMD already at the early stages of these diseases.

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