PMG-AD

Protective variant in PLCγ2 mitigates Alzheimer's disease-associated pathologies via enhancing beneficial microglia functions

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Aims, research questions and working hypothesis
PLCγ2-P522R (phospholipase C gamma 2, proline 522 to arginine) is a protective variant that reduces the risk for late onset Alzheimer's disease (AD). Recently, it was shown to decrease β-amyloid pathology in 5XFAD mouse model of AD. In this study, our goal was to investigate the protective functions of PLCγ2-P522R variant in a less aggressive mouse model of AD as well as to assess the underlying mechanisms at the molecular and cellular level using mouse and human microglia models.

Means/methods implemented by the consortium
The effects of the protective PLCγ2-P522R variant on microglia activation, AD-related β-amyloid and neuronal pathologies, as well as behavioral changes were investigated in PLCγ2-P522R knock-in mice crossbred with APP/PS1 AD model mice. Transcriptomic, proteomic, and functional studies were carried out in cultured and acutely isolated adult PLCγ2-P522R mouse microglia to study molecular mechanisms. Finally, microglia-like cell models generated from blood and skin biopsy samples of the PLCγ2-P522R variant carriers were employed to translate the key findings to human cells.

What are the outcomes of the project?
Our results demonstrate that the PLCγ2-P522R variant reduced brain β-amyloid plaque burden of APP/PS1 mice. Simultaneously, PLCγ2-P522R variant increased non-proinflammatory microglia activation and microglia clustering around β-amyloid plaques, leading to reduced β-amyloid plaque-associated neuronal dystrophy. In cultured mouse primary microglia, PLCγ2-P522R variant decreased accumulation of large lipid droplets, reduced cell stress, and increased acute response to strong inflammatory stimuli. Transcriptomic and proteomic analyses in acutely isolated adult mouse microglia as well as in human monocyte-derived microglial cells showed that PLCγ2-P522R upregulates mitochondrial fatty acid oxidation and downregulates inflammatory/interferon signaling pathways. Accordingly, PLCγ2-P522R increased mitochondrial respiration in iPSC-derived microglial cells.

Significance and impact of the work on the field
Together, these findings suggest that PLCγ2-P522R variant exerts protection against AD-associated β-amyloid and neuronal pathologies via enhancing microglial barrier formation around β-amyloid plaques and suppressing pro-inflammatory activation. Observed changes in fatty acid metabolism and mitochondrial flexibility as well as the downregulation of genes involved in inflammatory signaling pathways suggest that these protective effects of the PLCγ2-P522R variant are mediated through an anti-ageing mechanism.

Next steps and future challenges
Comprehensive functional and mechanistic characterization of PLCγ2-P522R with special emphasis on pathways and functions driven by lipid metabolism in cultured mouse primary microglia upon different stress conditions associated with aging and AD, and evaluation of the translational potential of findings in human microglial cell model.