

DACAPO-AD: Deciphering Interactions of Acquired Risk Factors and ApoE-mediated Pathways in Alzheimer's Disease

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The risk for developing late-onset Alzheimer's disease (AD) is strongly amplified by the apolipoprotein E (ApoE) e4 genotype, as well as by environmental and acquired risk factors. The ApoE-e4 polymorphism as well as the acquired risk factors are highly prevalent in the general population. However, the interactions between inherited and acquired risk factors have largely remained unexplored, mostly because animal models that adequately reflect the complex interplay between these factors are missing.

We therefore aimed to characterize the role of ApoE-e4 in AD pathogenesis by assessing amyloid metabolism and clearance, inflammation, neuronal and glial network dysfunction, astrocyte and pericyte dysfunction, and behavioral changes in an AD mouse model expressing human ApoE-e4 or wildtype mouse ApoE. We also aimed to expose these lines to acquired risk factors such as the western diet to determine if and how neurodegeneration and cognitive decline are accelerated following a combined impact of genetic and environmental risk factors.

We here found that the presence of the ApoE-e4 genotype had strong, previously unrecognized influences on several aspects of pathology in the APP/PS1 model of AD. In particular, i) ApoE-e4 altered cerebral network activity, measured using two-photon microscopy of cortical and hippocampal calcium changes; ii) the glymphatic distribution of ApoE-e4 differed significantly compared to ApoE-e2 and e3; iv) glymphatic and lymphatic clearance mechanisms were strongly reduced in double-transgenic ApoE-e4::APP/PS1 mice; iv) ApoE-e4 accelerated the deficits in electrophysiological correlates of plasticity and learning and memory, as assessed by hippocampal long-term potentiation and basal synaptic transmission. Importantly, many of these changes were aggravated in mice on a western diet compared to standard diet, indicating that environmental and inherited factors interact to shape disease progression in AD. We are currently investigating the molecular pathways underlying these interactions using single-cell RNAsequencing and other approaches.