Alzheimer's disease

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Studying microglia's role in APOE4-related pathology

The Apolipoprotein E ε4 allele, encoding APOE4, is the strongest genetic risk factor for late-onset Alzheimer's disease (AD). Evidence suggests that APOE4 contributes to AD by influencing amyloid-β (Aβ) and tau pathologies, but the underlying mechanisms are unclear. Similarly, while recent findings indicate that microglia — the resident immune cells of the brain — may interact with neurons to affect AD pathology, the effects of microglia on neuronal APOE4-related AD pathogenesis remain elusive. A study using chimeric mice with human APOE4 neuron transplants brings new insights into the role of neuronal APOE4 and microglia in AD pathogenesis.

While mice express only one form of APOE, in humans there are three predominant APOE alleles, which encode APOE2, APOE3 and APOE4 and confer varying levels of disease risk. Several in vivo models have been developed to study the role of these human APOE isoforms in AD, including human APOE knockin or transgenic mice. However, these models often also carry early-onset AD mutations to trigger pathology (such as Tg2576, APP/PS1 and 5xFAD mice) and lack human-specific disease features. To overcome these limitations, Huang's lab at Gladstone Institutes developed few years ago a chimeric model in which they transplanted induced pluripotent stem cell (iPSC)-derived human neurons carrying human APOE3 or APOE4 isoforms into the hippocampus of human APOE3 or APOE4 knockin mice (hE3-E3KI and hE4-E4KI mice, respectively). Chimeric hE4-E4KI mice, which do not carry early-onset AD mutations, develop Aβ aggregates in their brain, making them a suitable model to study human late-onset AD.

In their new study, the team combined the use of this human–mouse chimeric model with a microglial-depletion approach to investigate the role of microglia in human neuronal APOE-driven AD pathology. They found that removing microglia in hE4-E4KI mice reduced Aβ and tau aggregates. This finding suggests that microglia promote human neuronal APOE4-related brain pathology. Transcriptomic analysis revealed that in return, neuronal APOE4 promotes a pro-inflammatory response in microglia, thereby demonstrating the concerted roles of neuronal APOE4 and microglia in AD pathogenesis.

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