Investigating the Role of ApoE in Alzheimer's Disease

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Abstract:

Alzheimer's disease (AD) is a neurodegenerative disease and the most common form of dementia, characterized by impairment of memory and cognition. The etiology of AD remains unknown, however primary pathological features identified during disease progression include extracellular amyloid-β (Aβ) plaques, intracellular neurofibrillary tau tangles, synapse deterioration, neurodegeneration, and neuronal death. Apolipoprotein E (ApoE) is a cholesterol carrier that plays an important role in Aβ metabolism. Inheritance of certain ApoE polymorphic variants is a major genetic determinant of developing sporadic AD. There are three allelic variants of ApoE in humans: E2, E3, and E4. Individuals carrying the E2 allele have a two-fold decreased risk of AD, whereas carriers of one copy of the E4 allele have a three- to five-fold increased risk of AD, and those with two copies of E4 allele have an over ten-fold increased risk of AD compared to carriers of the E3 "normal" allele. Evidence suggests that ApoE isoform-dependent clearance and aggregation of Aβ accounts for the varying degrees of AD risk associated with inheritance of each allele. Current models propose that ApoE4 binds to Aβ and catalyzes its conversion to toxic Aβ filaments, leading to eventual neurodegeneration and cell death. Due to the critical contribution of ApoE to AD pathogenesis, future therapies targeting ApoE activity may be effective for alleviating or preventing AD progression. Through the use of cerebral organoids and ApoE4 assay screening, we will investigate potential molecules that target ApoE4 and have potential therapeutic function through the disruption of ApoE activity.