Group #23

Modeling APOE Genotype-Specific Alzheimer's Disease Pathology Using Isogenic iPSC-derived Brain Organoids

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Abstract

APOE ε4 is the strongest genetic risk factor for sporadic Alzheimer's disease (sAD), whereas ε2 is considered protective. However, there remains a critical need for human-relevant experimental models to investigate the mechanisms underlying these genotype-specific effects. To address this need, isogenic human brain organoids carrying APOE ε2/ε2 and ε4/ε4 alleles were generated and exposed to human serum to induce sAD-associated pathology, with a total of nine organoids analyzed for each genotype. APOE ε4 significantly exacerbated amyloid and tau pathology, with ε4 organoids exhibiting increased amyloid-β aggregation and tau tangle formation compared to ε2 organoids. These findings demonstrate that isogenic APOE brain organoids successfully recapitulate genotype-specific effects in sAD pathology, providing a promising human in vitro platform for future studies investigating APOE-mediated mechanisms.