Team23: Modeling APOE Genotype-Specific Alzheimer's Disease Pathology Using Isogenic iPSC-Derived Brain Organoids

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INTRODUCTION

Alzheimer's Disease (AD)
·Leading cause of dementia
·Hallmark pathologies:
- Amyloid-β (Aβ) plaques
- Neurofibrillary tangles (phosphorylated tau)

Apolipoprotein (APOE)
·Lipid transport protein in the brain
·Strong association with sporadic AD risk
·Genotype-specific effects:
- APOE ε2: protective
- APOE ε4: most risky

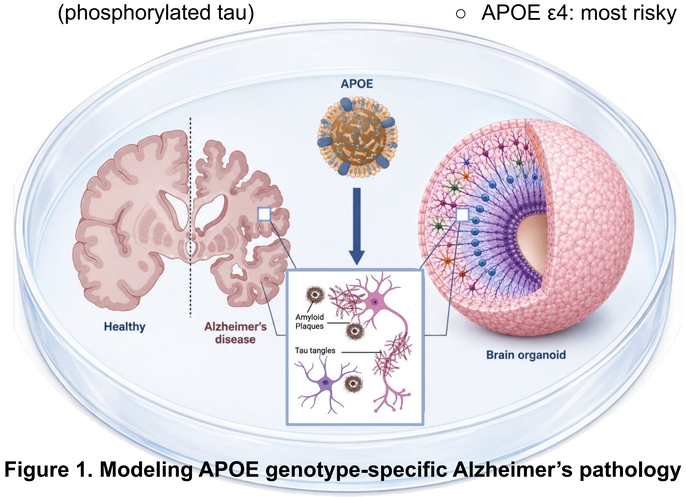


Figure 1. Modeling APOE genotype-specific Alzheimer's pathology

Brain Organoids (BOs)
·3D iPSC-derived neural tissues ("mini-brains")
·Recapitulate key aspects of human brain development, structure, and functional neural networks.
·Enable in vitro modeling of human neurodegenerative disease.

→ **Research Question:**
Can we model APOE genotype-specific effects in sporadic Alzheimer's pathology using human brain organoids?

METHODOLOGY

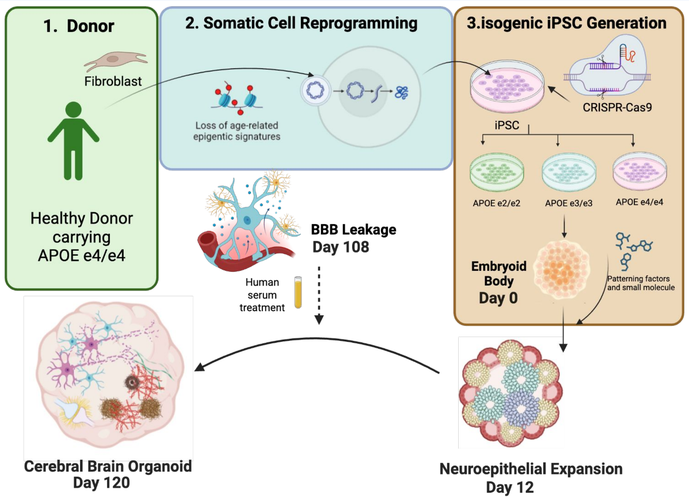


Figure 2. Generation of isogenic APOE brain organoid models for sporadic Alzheimer's disease modeling

RESULT

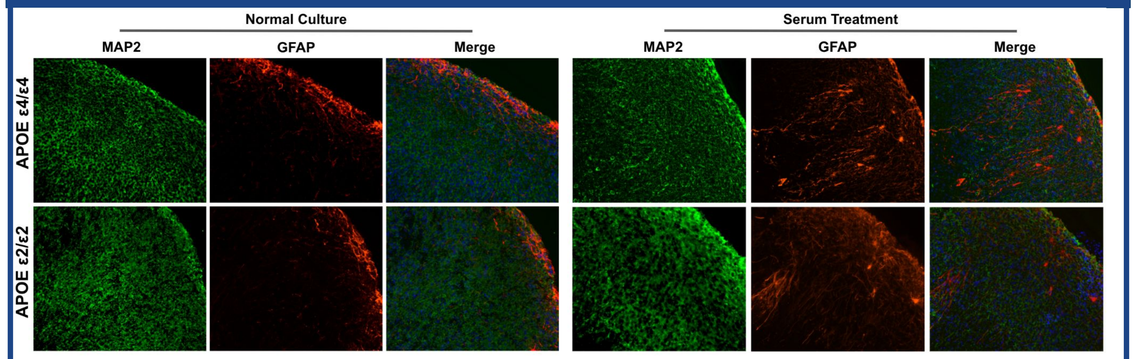


Figure 3. Representative DAPI and immunofluorescence images of MAP2+ neurons and GFAP+ astrocytes in 120-day BOs.

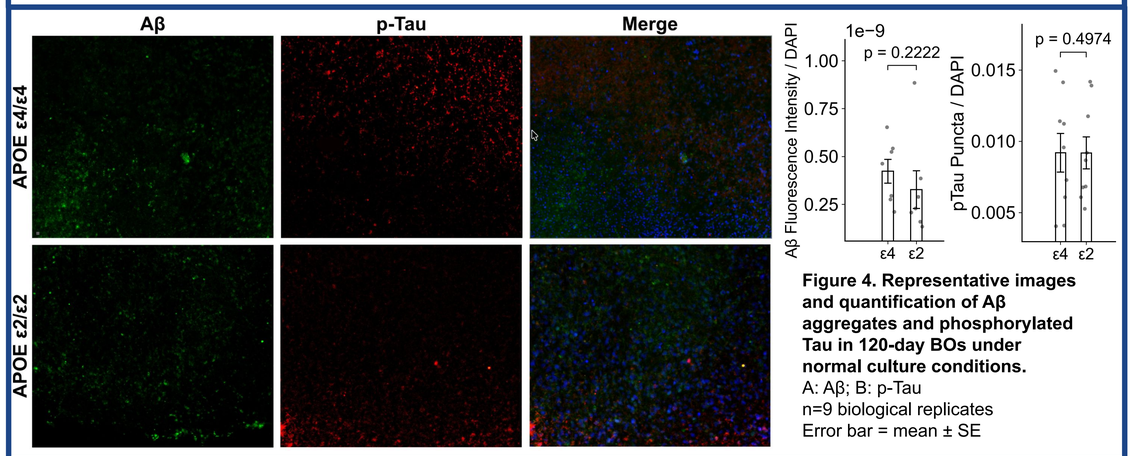


Figure 4. Representative images and quantification of Aβ aggregates and phosphorylated Tau in 120-day BOs under normal culture conditions.
A: Aβ; B: p-Tau
n=9 biological replicates
Error bar = mean ± SE

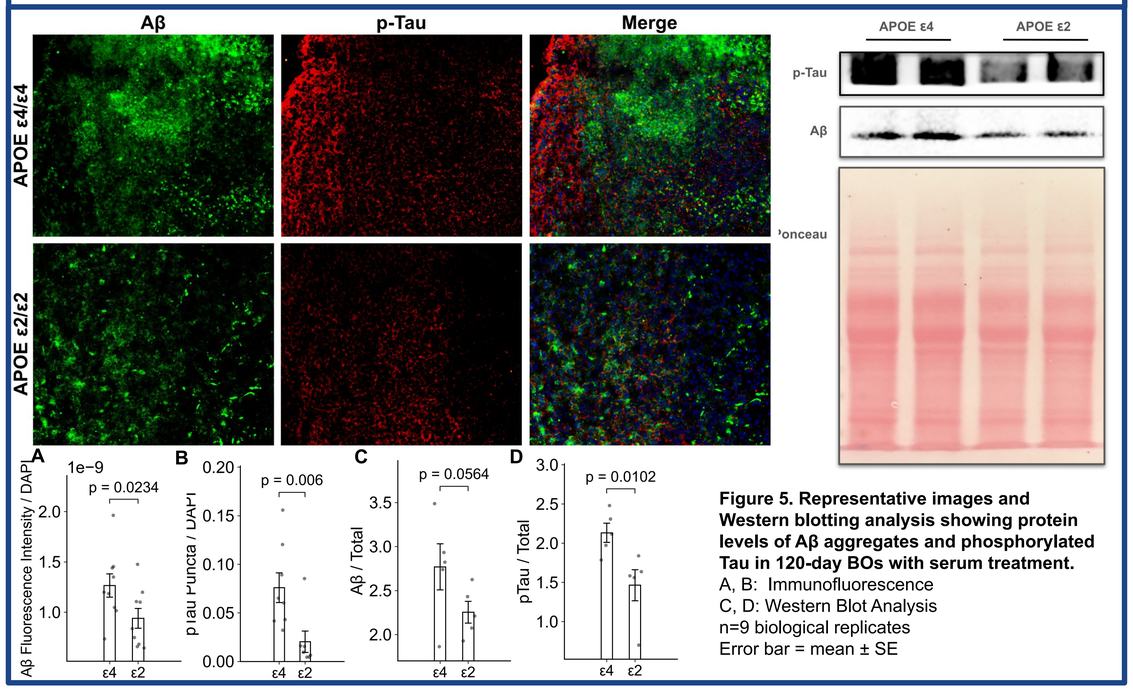


Figure 5. Representative images and Western blotting analysis showing protein levels of Aβ aggregates and phosphorylated Tau in 120-day BOs with serum treatment.
A, B: Immunofluorescence
C, D: Western Blot Analysis
n=9 biological replicates
Error bar = mean ± SE

DISCUSSION

Quality Check
· All groups exhibit key cellular components (neurons + astrocytes) and preserved cytoarchitecture.
· No significant structural differences across APOE genotypes or serum conditions.

APOE genotype-dependent differences in AD pathology are modest in the absence of serum treatment at day 120.

APOE ε4 exacerbates amyloid and tau pathology in sporadic AD organoid model.
· Under serum + conditions, APOE ε4 organoids show significantly increased Aβ and p-tau compared to ε2.
· Indicates enhanced vulnerability of ε4 under pathological conditions.

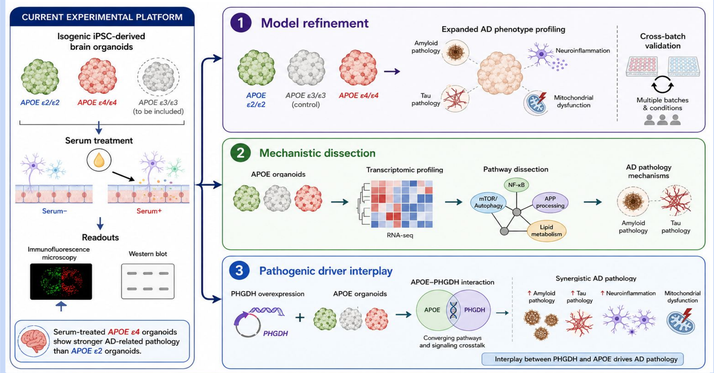
Overall, serum-treated organoids recapitulate APOE-genotype -dependent AD phenotypes, providing proof of concept for modeling of APOE biology in sporadic AD.

FUTURE DIRECTIONS

Model refinement
· Include APOE ε3 organoids as a control group.
· Assess additional AD-associated phenotypes, such as synaptic loss.
· Validate findings across additional batches and conditions.

Mechanistic dissection
· Examine APOE genotype-specific transcriptomic signatures
· Dissect molecular pathways underlying APOE-induced pathology.

Pathogenic driver interplay
· Introduce PHGDH overexpression in APOE organoids.
· Examine interplay between PHGDH and APOE in modulating AD pathology.



ACKNOWLEDGEMENT

Design Website
References

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