Poster

Use of brain organoids for the development of new treatments for Amyotrophic Lateral Sclerosis (ALS)

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ABSTRACT

Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disease with no cure, leading to patient death within 2-5 years after symptom onset. As a result, there is a loss of muscle strength that spreads, affecting mobility, speech, swallowing, and breathing, while the senses, intellectual capacity, and eye muscles remain unaffected. Many drugs showing promising results in animal models failed in clinical trials, likely due to poor predictability of human brain responses. Developing more predictive models based on human cells is crucial to advance our understanding of ALS pathophysiology and promoting the development of more effective and safer therapies. Animal experimentation, while widely used, has significant limitationsfor the development of medicines targeting central nervous system and is increasingly questioned for ethical and scientific reasons. In response, brain organoids have emerged as a promising alternative (García-Delgado et al; 2022). Here we show a way to generate a robust ALS model using cortical organoids derived from induced pluripotent stem cells (iPSCs). To enhance model reliability, we have applied a small-molecule-guided protocol that reduces heterogeneity and improve cortical specificity. We applied dual SMAD inhibition using SB431542 and Dosomorphin to reduce non-ectodermal contamination and improve cortical specification. Additionally, we incorporated decellularized extracellular matrix (cECM) (Cho et al; 2021)derived from ALS patients and healthy controls. Cortical-derived cECM, rich in proteoglycans, laminins, and integrins, better mimics the neural niche, enhancing neural differentiation and maturation compared to conventional matrigel (García-Delgado et al; 2024). These advancements establish a highly predictive ALS model for evaluating drug efficacy and safety, driving the development of novel therapies and optimized drug delivery strategies.

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