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Poster P10

Modelling YARS-Related Charcot-Marie-Tooth Disease: Establishing a Link Between YARS1-related Neurodegeneration and Mitochondrial Dysfunction

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Dominant intermediate CMT type C (DI-CMTC) has been linked to mutations in the YARS1 gene, which encodes tyrosyl-tRNA synthetase. Emerging evidence suggests that YARS mutations cause neuropathy through a toxic gain-of-function mechanism affecting transcription, axonal transport, and actin dynamics. While previous studies showed altered mitochondrial morphology in YARS-mutant fibroblasts, a functional motor neuron-based model to assess mitochondrial involvement in DI-CMTC has been lacking. In this project, motor neurons were generated from iPSCs derived from four distantly related YARS E196K patients and corresponding isogenic controls. To examine axonal phenotypes, neurons were cultured in Xona Microfluidic Devices, enabling compartmentalisation of proximal and distal axons. Live-cell imaging was performed on day 28 post-differentiation to visualise organelles movement. Mitochondrial morphology was assessed using both immunofluorescent staining and live MitoTracker imaging in 2D and 3D cultures. To assess neuronal identity, Islet-1-positive nuclei were quantified across patient and control lines. Also, cellular stress was modelled by treating neurons with sodium arsenite. Motor neuron differentiation efficiency was comparable between YARS-mutant and control lines, confirming the mutation does not impair neural development. However, mitochondrial morphology analysis revealed an increase in fragmentation and decreased size in the distal but not the proximal compartments of YARS-mutant neurons. Live imaging demonstrated a selective reduction in mitochondrial transport velocity in distal axons. Additionally, stress granule analysis showed smaller G3BP1-positive granules in mutant neurons following oxidative stress, pointing to an altered stress response. Our findings describe how YARS mutations cause distal axonal degeneration that disrupts mitochondrial trafficking and morphology, and suggest mitochondrial dynamics as a potential therapeutic target.