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Using induced pluripotent stem cells (iPSCs) to model mitochondrial disease, study tissue specific manifestations and investigate treatments

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The inability to replicate mtDNA caused by mutations in the POLG gene leads to a subset of mitochondrial diseases. POLG mutations can cause neuronal death and neuronal depletion of mtDNA. While informative, post-mortem studies often represent the end stage of disease and are not tractable. The need for models to study disease mechanisms is, therefore, clear and since mouse models often fail to recapitulate the human neural phenotype, we chose to examine the potential of induced pluripotent stem cells (iPSCs). IPSCs retain the potential to differentiate into any cell type and, while still at an early developmental stage, carry the disease mutation and the patients' own genetic background, giving us the possibility to study disease during tissue development. In our lab, we reprogrammed patient fibroblasts carrying the two common POLG mutations (c.2243G>C; p.W748S and c.1399G>A; p.A467T) into iPSCs. We have established the robust protocols and model systems based on iPSC-derived brain cells, including neural stem cell (NSCs), generic neurons, dopaminergic (DA) neurons, astrocytes, and oligodendrocytes. We further developed 3D spheroid and DA neurons / astrocytes in-direct co-culture model, allowing us to explore the interaction of different brain cells carrying POLG mutation comparing to healthy individuals. We have generated compelling evidence of the multiple cellular and molecular mechanisms contributing to the decline of mitochondrial dysfunction observed in NSCs, DA neurons and astrocytes derived from POLG-iPSCs and open the possibility to identify novel molecules actively involved in the process that could ultimately lead to a deeper characterization and novel therapeutic targets for neurodegeneration.

Biography

Kristina Xiao Liang a Senior Researcher, group leader in stem cell research in Mitochondrial Medicine & Neurogenetics (MMN) group University of Bergen, Norway. Her research theme is to use human iPSCs to model mitochondrial diseases with POLG mutation. Specifically, her research interests include establishment of neural differentiation from human iPSCs, using iPSCs-derived neural stem cell, dopaminergic neurons, astrocytes, and 3D brain organoids to model mitochondrial disorders, and further explore their mitochondrial functions, mitochondrial biogenesis, and metabolic features to understand the mechanism of mitochondrial diseases. Her research involves a wide range of stem cell biology, cell metabolism, neurobiology, mitochondrial dynamics. She has been involved in the development and use of different kinds of iPSCs derived neuronal cell culture models, characterizing mitochondrial related properties, the interaction of glial cells (astrocytes) and neurons and their mitochondrial transfer and metabolic revolution. She has published more than 23 papers in reputed journals and her work has been published in high impact journals including EMBO molecular medicine, Cancer Research and Cellular and Molecular Life Sciences et al.