10th International Tissue Repair and Regeneration Congress
12th Annual Conference on Stem Cell and Regenerative Medicine
&
International Conference on Cell Biology and Genomics
June 13-14, 2019 Helsinki, Finland

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Induced pluripotent stem cell models for Alzheimer's disease

Alzheimer's Disease (AD) is the most common cause of dementia with currently no curative treatments available. To combat this disease it is crucial to understand the precise cellular disease pathology in order to define new targets for intervention. We have built a human induced pluripotent stem cell platform enabling us to study the disease mechanisms in the relevant target cells: human neurons, astrocytes and microglia. Our focus is on PSEN1, APP and sporadic forms of AD. For all of our lines with defined mutations we have generated *CRISPR-Cas9* gene edited controls replacing the mutant nucleotide and generating isogenic controls. Our studies have so far revealed abnormal cristae formation in mitochondria accompanied by aberrant mitochondrial distribution and mitochondrial respiration deficiency. Other cellular phenotypes revealed abnormal ultrastructure's of the Golgi Apparatus (GA), with shortened and dilated cisternae and increased surface area. The GA's were scattered around the nuclei, indicating GA fragmentation. Furthermore reduced synaptic density and glutamine metabolic defects were part of the disease phenotypes. All of the observed cellular phenotypes were rescued in *CRISPR-Cas9* generated isogenic controls, indicating a clear connection to the mutation. Moreover, mitochondria deficits, metabolic disturbances and synaptic deficiencies are considered early disease phenotypes, which can be recapitulated in our *in vitro* patient specific disease models making them attractive for drug target development for early interventions.

Biography

Kristine Freude is an Associate Professor at the University in Copenhagen and Director of the Center for Excellence in Neuroscience BrainStem. She has been at the University of California at Irvine, where she received her training in Stem Cell Biology funded by the California Institute for Regenerative Medicine (CIRM). Her current research is focused on disease modeling using induced Pluripotent Stem Cells (iPSC) from patients with neurodegenerative diseases such as Alzheimer's as well as *CRISPR-Cas9* gene edited iPSCs carrying mutations associated with neurodegenerative diseases. Her research is funded by Innovation Foundation Denmark, Novo Nordisk Foundation and the Danish Alzheimer's Foundation.

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