Research project:

Modelling the molecular pathogenesis of ARSACS with patient cells: disrupted proteostasis in ARSACS neurons

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Scientific Summary

Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) is a childhood-onset neurological disease, with pyramidal spasticity and cerebellar ataxia. ARSACS results from mutations in the SACS gene encoding sacsin. Although sacsin has been associated with mitochondria and contains domains linking it to molecular chaperones and the ubiquitin proteasome system, pathophysiological mechanisms of ARSACS are poorly understood.

We have identified that systems responsible for the clearance of aberrant protein species are disrupted in sacsin knockdown cells and fibroblasts from ARSACS patients. This includes evidence for the presence of aggresomes, which form when cellular systems that deal with misfolded proteins become overwhelmed.

This proposal will test if the observed structures are indeed aggresomes and define how systems that deal with removal of misfolded proteins are disrupted in ARSACS. This will include the identification of protein/s that abnormally accumulate in sacsin knockdown cells and patient fibroblasts. We will then test if there is evidence for accumulation of aberrant protein species and disruption of proteostasis systems in induced pluripotent stem cell (iPSC) derived human neurons that lack functional sacsin.

Defining the molecular pathogenesis of ARSACS is valuable as it represents the first step in identifying a therapeutic strategy for this ataxia.

Lay Summary

The study aims to understand the cellular defects that lead to ARSACS. Like other ataxias, ARSACS is a neurodegenerative disease, which means brain cells (neurons) die as the disease progresses. It is not completely clear what causes neurons to die in most neurodegeneration, but one factor that has been identified as common to a number of diseases, is the accumulation of damaged proteins that may be toxic or disrupt normal cellular processes.

This study aims to build on the extensive preliminary data in which the team have identified that the cellular systems that deal with the disposal of damaged proteins may be perturbed in ARSACS. The aim of this project is to investigate this further by working

out exactly what has gone wrong with the cellular machinery that normally deals with the disposal of these unwanted proteins.

ARSACS is not well studied and current treatments for this childhood onset disease are largely symptomatic. This research will provide some of the initial clues of what goes wrong in ARSACS and should represent the first step in identifying a therapeutic strategy. Moreover, understanding ARSACS may give insights into other ataxias as they may share common disease mechanisms.

This project is co-funded with the ARSACS Foundation

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