“Molecular characterisation of sacsin deficient cells”

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Our current focus is completion of a comprehensive molecular characterisation of neuronal cells that have been genetically engineered so that they no longer express sacsin, the protein that is mutated in ARSACS. We have used what are known as ‘omics’ technologies to look at the molecular differences between control cells that have the sacsin protein and cells where it has been ‘knocked out’ as a model for disease. This work has been in collaboration with Dr. Justin Wolter at the University of North Carolina.

Specifically, our research groups have performed quantitative analyses to find any differences in gene transcription (transcriptomics), proteins present in the cell (proteomics) and whether these proteins have regulatory modifications known as phosphorylation (phospho-proteomics). We have also looked at difference in cell surface expression of proteins and catalogued which other proteins interact with sacsin, to define its ‘interactome’.

These data have allowed us to further understand aspects of the ARSACS cellular phenotype that we have been investigating. This includes impaired formation of structures called focal adhesions that are important for the interaction between cells and their surrounding extracellular matrix, where we have now discovered that proteins integral to focal adhesion signalling, known as integrins, are mislocalised in the absence of sacsin. This is potentially important for ARSACS as disruption of focal adhesions and integrin function may impact the formation of neuronal synapses, with the Wolter lab showing this to be the case in an ARSACS mouse model.

Our molecular characterisation has also provided clues to the mechanisms which underly previously reported cytoskeletal phenotypes in sacsin knockout cell, supporting the hypothesis that transport along microtubules is disrupted. Currently the Chapple lab is further interrogating the omics data sets to increase our understanding of what goes wrong at the cellular level when sacsin function is impaired. We are also adding to this data by quantifying changes in cellular metabolites that are associated with sacsin loss. Importantly all our omics data is being made publicly available as a resource for the ARSACS research community. Overall, these studies are helping us identify commonalities in disease mechanism between ARSACS and other neurodegenerative conditions that may ultimately inform the development of therapies.

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