## Metabolic rewiring in cellular models of ARSACS: Progress report, November 2023

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The viability of neurons in the brain depends on a complex series of interconnected biochemical reactions that constitute cellular metabolism. Disruption of these metabolic pathways is associated with neurological conditions, including Alzheimer's. Recent technical advances in the analysis of cellular metabolites mean it is now possible to simultaneously quantify the levels and turnover of multiple metabolites in cells. We are using this technology to compare the metabolite profiles of control cells and cells that lack the protein sacsin, which is mutated in ARSACS. Disruption of cellular metabolism is likely to be particularly relevant to ARSACS because it has previously been shown that the health of mitochondria, organelles where key metabolic enzymes are located, is reduced in cellular and animal models of ARSACS. Our goal is to define the metabolic changes that occur in sacsin deficient cells as we believe this will elucidate ARSACS disease mechanism and potentially identify targets for therapeutic intervention. Through this research we have identified disturbance in levels of metabolites mitochondria produce. This includes for a series of biochemical reactions called the TCA cycle that is key to making other metabolites and the fuel, ATP, which cells run on. We also find disruption of glutamine-glutamate metabolism in cells lacking sacsin. Glutamate can be made from glutamine and these metabolites are important for brain function as glutamate acts as a neurotransmitter, carrying messages between neurons. Thus, a key current objective for the work is to understand why glutamine-glutamate metabolism is altered and whether this is relevant for ARSACS. At the start of the project, we performed pilot experiments in cultured (grown in dishes in the lab) cells where we had used a genetic technique to remove sacsin. Then, over the last 12- months of the project, we have been making the research more relevant to what happens in the human brain by performing analysis in sacsin deficient cells we have treated to become more like neurons. This has revealed multiple metabolic changes, associated with loss of sacsin, some of which are specific to the more neuronal cells. We are currently working to understand the relevance of these metabolic alterations to ARSACS.