“Unraveling the role of glial cells in ARSACS Rationale”

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Abstract

The final goal of our project is to unravel the potential role of glial cells in ARSACS. Our original hypothesis is supported by our findings: 1) astroglial and microglial cells express high levels of sacsin and 2) the cortex of sacsin knockout mice have a higher expression of astroglial, oligodendroglial and microglial markers. We performed CRISPR/Cas9 deletion of sacsin in human glial cell lines, and our preliminary results indicate that human glial cell models of ARSACS resemble the rat C6 glial cell models of the disease previously developed in our laboratory (Murtinheira et al. Cells, 2022). Proteome analysis of sacsin-knockout rat C6 glial cells identified alterations in proteins involved in cell development/differentiation or organelle organization, which are currently under study in both rat and human astroglial cell models of ARSACS as well as sacsin knockout mice. In parallel, we are developing a pharmacological model of ARSACS, based on the treatment with Withaferin A. Most cellular models of ARSACS -neural, glial or otherwise- display disorganization or aberrant morphologies of intermediate filaments. Withaferin A is an inhibitor of type III intermediate filaments, and we are characterizing the cellular and molecular alterations caused by this drug in wild-type cells and zebrafish. Wild-type C6 glial cells treated with Withaferin A are more sensitive to stress and show perinuclear accumulation of glial intermediate filaments, resembling the phenotype of sacsin-negative C6 glial cells. However, in other aspects, Withaferin A incubation does not mimic sacsin loss. This approach could provide relevant information about which aspects of ARSACS are due to intermediate filament disorganization and which are caused by other mechanisms. Our glial cell and pharmacological models of ARSACS could help to understand how this disorder affects a significant part of the brain glial cell population and viceversa: how glial cell dysfunction could contribute to ARSACS.

March 30,2023