Towards glial-targeted therapies of ARSACS

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ARSACS symptoms clearly point at dysfunctions in the neuronal circuits in the cerebellum, especially in a population of cerebellar neurons known as Purkinje cells. Purkinje cells contain high levels of sacsin, the protein mutated in ARSACS, and sacsin´s loss of function could be especially deleterious for them. And yet, the populations of glial cells essential to support and protect neurons also contain high levels of sacsin, and some pathological features of ARSACS are similar to disorders involving glial dysfunction, neuroinflammation and loss of white matter. In this project, we investigated the possible alterations caused by sacsin loss in these populations of glial cells. We have found that there are alterations in the number and role of glial cells in the ARSACS nervous system. There are strong signs of neuroinflammation and anatomical alterations consistent with neurodegeneration not only in the cerebellum, but also in the cortex. We have developed two genetic models of ARSACS in glial cells, based on the inactivation of the sacsin gene, and a third one based on a natural drug (withaferin A) that produces effects on cells similar to sacsin deletion. Our results indicate that inactivation of sacsin in glial cells produces defects that are very similar to those found in ARSACS neurons. Sacsin loss of function causes disorganization of the basic cellular structure, and renders glial cells more sensitive to mechanic, chemical and starvation stress, increases the levels of proteins involved in neuroinflammation (e.g. S100B), and decreases the levels of proteins essential for protection against stress and oxidative damage (e.g. ERO1, LC3) and for neural development (e.g. STAT3, Smad1). Some of these results were also observed in mouse models of ARSACS, and we also set up a zebrafish model of ARSACS to confirm whether these alterations are universal to all models of the disease. These models will be later used to test therapeutic strategies that prevent the pathological features of ARSACS. Some of them could be specifically targeted at non-neuronal populations of the nervous system – the glial cells.