41 A pharmacological treatment acting on calcium homeostasis improves motor ability and delays Purkinje cell loss in the ARSACS mouse model

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Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) is a childhood-onset cerebellar ataxia caused by loss-of-function mutations in *SACS* gene. *SACS* encodes sacsin, a cytosolic protein mainly expressed in neurons with the highest levels in Purkinje cells. Loss of Purkinje cells is indeed the most prominent feature of ARSACS patients and of the *Sacs*$^{-/-}$ mouse model. To date, sacsin function remains largely unknown and no treatments are available for ARSACS.

We and others have identified the remodelling of intermediate filament-cytoskeleton as one of the earliest consequences of sacsin absence. Both vimentin (in ARSACS patient fibroblasts) and neurofilaments (in neurons) accumulate in the absence of sacsin, forming atypical dense bundles. Remodelling of the intermediate filament cytoskeleton is known to affect mitochondrial distribution in different cell types. We thus hypothesized that abnormal neurofilament accumulation in the absence of sacsin may oppose to mitochondrial trafficking on microtubules, thus favouring mitochondrial docking. In agreement, we demonstrated that mitochondrial transport is altered in distal processes of *Sacs*$^{-/-}$ cultured primary Purkinje cells, which show a significant retention of mitochondria in the soma compared to the wild-type. Likely as consequence of defective mitochondrial transport, we found a deregulation of calcium homeostasis in *Sacs*$^{-/-}$ cerebellum, both *in vitro* and *in vivo*. In fact, mitochondria provide ATP to active calcium clearance systems at the plasma membrane and endoplasmic reticulum, but also exert themselves a fine shaping of calcium signals by accumulating calcium into the matrix.

We demonstrated that a pharmacological treatment with an off-label drug favouring the synaptic glutamate clearance attenuates motor symptoms and delays PC degeneration in *Sacs*$^{-/-}$ mice, at pre-symptomatic stages as well as post-symptomatic stages. This treatment may represent a therapeutic option for diagnosed pre-symptomatic ARSACS patients, but also for patients with overt symptoms.

Our data suggest the deregulation of calcium homeostasis as a crucial feature of ARSACS pathogenesis and offer perspectives for disease treatment.