Unraveling the physiopathological role of sacsin, the protein mutated in autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS).

ARSACS is the second most common form of recessive spastic ataxia after Friedreich’s ataxia and is characterized by childhood onset progressive neurodegeneration primarily involving cerebellum and corticospinal tract. More than 70 ARSACS-causing mutations have been identified worldwide in the SACS gene, most of which are frameshift, nonsense or macrodeletions (Synofzik M et al, 2013). The SACS gene encodes the massive 520kDa protein sacsin, whose cellular function is still largely unknown. Sacsin is a multimodular protein composed of a ubiquitine-like domain that binds to the proteasome, three regions with similarity with the N-terminal domain of Hsp90 and a DnaJ domain that binds Hsc70, suggesting that sacsin may operate in protein quality control (Parfitt DA et al, 2009; Anderson JF at al, 2011). Sacsin is predominantly cytosolic, but co-localizes partially with mitochondria, likely associating to the outer mitochondrial membrane. The quantitative analysis of mitochondrial morphology in ARSACS patient fibroblasts, in which we detected dramatically reduced levels of sacsin, revealed a markedly higher number of cells displaying a fused and interconnected network with extremely long tubules compared to controls. These data indicate that loss of sacsin function leads to enhanced fusion or decreased fission of mitochondria, even if the molecular mechanism underlying this phenotype remains to be clarified. Also, we found that cells lacking sacsin display evident signs of cell stress, at both morphological and biochemical level. Aims of the PhD project are (i) to study the still unexplored role of sacsin in cellular physiology and (ii) to define the mechanisms by which its absence causes perturbation of mitochondrial dynamics and cell stress. To this end, we will apply integrated approaches of cell biology and proteomics, which rely on already available in vitro models and patient samples. These studies will be instrumental to identify new cellular pathways in which sacsin is involved, with potential relevance for ARSACS therapy.