Altered mitochondrial dynamics is central to different genetic forms of cerebellar ataxias: dissecting the molecular pathogenesis in cellular and animal models.

Hereditary cerebellar ataxias are neurodegenerative diseases characterized by progressive incoordination of gait, hands, speech and eye movements due to degeneration of Purkinje cells (PCs) in the cerebellum. PCs are characterized by a large soma and extensive dendritic trees, which mainly receive glutamate excitatory stimulation and are exposed to high calcium concentrations.

Proper mitochondrial functionality and distribution to microdomains of large ion fluxes represent crucial issues in PCs. Indeed, mitochondria not only provide ATP to active calcium clearance systems, but also exert themselves a fine shaping of calcium signals by accumulating calcium into the matrix.

Mitochondria are dynamic organelles by several criteria. They engage in repeated cycles of fusion and fission (collectively called "mitochondrial dynamics"), which serve to intermix the lipids and matrix contents of a population of mitochondria in response to pathophysiological stimuli. In addition, mitochondria are actively recruited to subcellular sites, such as the axonal and dendritic processes of neurons.

The project aims at dissecting the molecular pathogenesis of two inherited forms of cerebellar ataxia, namely Spinocerebellar ataxia type 28 (SCA28) and autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS), which peculiarly have in common alterations of mitochondrial dynamics as the cause of PC degeneration (1-3). The main objectives are: (i) to define the molecular mechanisms leading to altered mitochondrial dynamics when the disease-gene is mutated; (ii) to investigate how perturbations of mitochondrial dynamics impact on mitochondrial trafficking and lead to PC degeneration. To this end, we will employ integrated approaches of imaging and biochemistry taking advantage of the already available SCA28 and ARSACS mouse models and of our established expertise in deriving primary PCs.

The identification of common pathogenetic pathways will be instrumental to develop target therapy at the mitochondrial level, which can be beneficial for both the diseases.