Project 2. Counteracting mitochondrial dysfunctions in neurodegenerative diseases (Group leader Jean-Charles Liévens)

Energy defects and increased oxidative stress resulting from **mitochondrial dysfunction** are key determinants in many neurodegenerative diseases. Our main objective is to find therapeutic targets to correct them. We are more particularly interested in two motor pathologies: ALS and **type 7 spastic paraplegia (SPG7)**.

1- ALS is due to the loss of motor neurons leading to the progressive paralysis of patients. Using genetic tools in Drosophila, we provided the first in vivo demonstration that the S1R could be a relevant target for preventing energy deficits and oxidative stress in ALS (*Couly et al., Hum Mol Genet 2020*; *Lee, Liévens, Wang et al., Nat Commun 2020*). A second therapeutic strategy that emerges from our work is to increase glucose metabolism (*Besson et al., PLoS One 2015*; *Manzo et al., ELife 2019*). Now we want to validate these targets and dissect their mechanism of action on vertebrate models of ALS in zebrafish or mice.

2- SPG7 is characterized by the presence of spasticity, cerebellar ataxia and chronic external ophthalmoplegia. It is due to the degeneration of the cortico-spinal pathway and cerebellum. SPG7 is an inherited disease caused by mutations in the spg7 gene encoding the mitochondrial protease, Paraplegin. However, while this disease is considered recessive, some clinical observations also argue for a detrimental impact of spg7 mutation at the heterozygous state. Our aim is to understand if the presence of a single mutated copy of spg7 acts as a predisposing risk factor for the development of neurological symptoms. The study focuses on fibroblasts obtained from skin biopsies of symptomatic patients with the spg7 mutation an the simple heterozygous state or homozygous/double heterozygous state and control individuals. In parallel, an analysis is also carried out in vivo on a model organism, Drosophila. The use of this genetic model allows the identification of genes and targets modifying the SPG7 pathology. In the longer term, they will be validated on zebrafish models.

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