Project 1. Deficit of communication between ER and mitochondria in neurodegenerative diseases. (Group leader Benjamin Delprat)

Wolfram syndrome is a rare disease characterized by diabetes, optic atrophy, sensorineural deafness, and cognitive and psychiatric deficits. We have shown that these symptoms were due to a **communication deficit between the endoplasmic reticulum and the mitochondria** at the level of the MAMs (membranes of the endoplasmic reticulum associated with the mitochondria). Very interestingly, this deficit is also found in other neurodegenerative (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis) and metabolic (diabetes, cardiomyopathy). Therefore, our goal is to understand the signaling pathways at the origin of this deficit and to identify new therapeutic strategies to restore this communication.

Mechanisms of impaired RE-mito communication in Wolfram syndrome.
WFS1, the protein deficient in Wolfram syndrome, interacts with NCS1 to modulate the number of contacts between the RE and the mitochondria but also the quantity of Ca^{2+} which will pass from the light of the ER to the matrix of the mitochondria (Angebault et al. Science Signaling. 2018). We recently demonstrated that the activation of sigma-1 receptor, a chaperone mainly expressed in the MAMs, is able to restore the cellular and behavioral deficits of our preclinical models (Crouzier et al., Science Translational Medicine. 2022). This exciting result opened the pathway toward a novel therapeutic strategy.

Towards the treatment of MAMpathies.
Ultimately, our goal is to restore these communication deficits in Wolfram syndrome first, then to decline our therapeutic solution to other pathologies of MAMs, MAMpathies. We already demonstrated that the overexpression of NCS1 is able to restore the cellular deficits in the fibroblasts of patients. Our goal is therefore to use an original gene therapy in mouse models of Wolfram syndrome. A second approach is based on screening a chemical library of active molecules (novel chemical entities or repositionable drugs) on a zebrafish model of Wolfram syndrome (Crouzier et al., Human Molecular Genetics. 2022)

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