Project 1. Communication deficit between ER and mitochondria in neurodegenerative diseases: from pathophysiology to therapy (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 ER and the mitochondria at the level of the MAMs** (membranes of the ER associated with the mitochondria). Quite interestingly, this deficit is also found in other neurodegenerative (AD, Parkinson's disease, ALS) and metabolic diseases (diabetes, cardiomyopathy). Our goal is to understand the signaling pathways at the origin of this deficit and to identify new therapeutic strategies to restore this communication. We have identified a cellular mechanism of impaired ER-mitochondria 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 are now investigating effective treatments of these 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 have the demonstration 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 (new chemical entities or repositionable drugs) on a zebrafish model of Wolfram syndrome.

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