ER-mitochondria crosstalk is regulated by NCS1 and is impaired in Wolfram syndrome

Benjamin Delprat¹, Claire Angebault¹, Jérémy Fauconnier², Simone Patergnani³, Jennifer Rieusset⁴, Dan Milea^{5,6}, Christian Hamel^{1,7}, Paolo Pinton³, Marc Thiry⁸, Alain Lacampagne², Cécile Delettre¹

¹Inserm U 1051, Institut des Neurosciences, Hôpital Saint Eloi, Montpellier, France, ²Inserm U1046, UMR CNRS 9214, University of Montpellier, 34295 Montpellier, France, ³University of Ferrara, Ferrara, Italy, ⁴INSERM U1060, UMR INRA 1397, Lyon, France, ⁵Angers University Hospital, France, ⁶Singapore National Eye Centre, ⁷CHU, Gui de Chauliac Hospital, Montpellier, France, ⁸Université de Liège, Belgium

Wolfram syndrome is a childhood onset rare genetic disease (1/180,000) featuring diabetes mellitus and optic neuropathy unavoidably progressing towards legal blindness before the age of 20. Here we show that WFS1 forms a complex with Neuronal Calcium Sensor 1 (NCS1) and IP3R to promote ER-mitochondrial Ca²⁺ transfer. In addition, we report that NCS1 localizes to mitochondria-associated membranes and regulates mitochondrial respiratory chain. Importantly, NCS1 overexpression not only restore ER-mitochondria interaction and Ca²⁺ transfer, but also induces a significant rescue of the dysfunctional mitochondrial phenotype observed in WFS1 deficient cells. Since NCS1 may be targeted by pharmacological molecules, it may be a useful target to treat Wolfram syndrome pharmacologically.