New findings on the function of mitofusin 2 in the cellular energy metabolism

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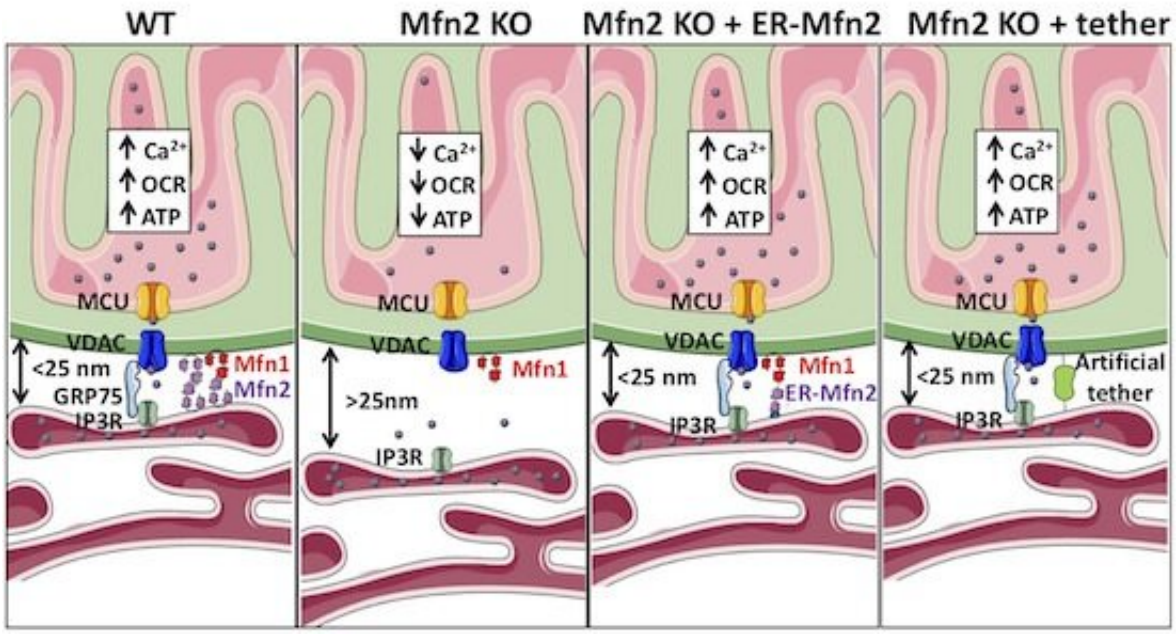

The Mfn2 has a mainly mitochondrial localization, but a small portion of the protein is also in the endoplasmic reticulum. Credit: University of Barcelona

Mitofusin 2 is a key protein in the regulation of the physiology of mitochondria—cellular organelles that produce energy—involved in several neurodegenerative and cardiovascular diseases, as well as in cancer. Now, a study published in the journal *EMBO Reports* reveals that the regulation of the bioenergetic activity in the mitochondria requires mitofusin 2 to be found in the endoplasmic reticulum, a system built by a complex network of membranes in the cell cytoplasm

The study is led by the lecturer Francesc Soriano, from the Faculty of Biology and the Institute of Neurosciences (UBNeuro) of the UB. Other co-authors of the paper are the experts Ofelia M. Martínez and Francesc Villarroya, from the Faculty of Biology and the Institute of Biomedicine (IBUB) of the UB, and Manuel Reina, from the same faculty, among others.

Mitofusin 2: A bridge between cell organelles

Mitofusin 2 (Mfn2) is a protein in the external membrane of the mitochondria with a distinguished role in several physiological processes: mitochondrial dynamics, energy metabolism, embryo development, cell death, etc. This essential protein in the morphology and function of mitochondria is involved in several pathologies related to dysfunctions in the production of mitochondrial energy. Therefore, understanding how Mfn2 regulates the mitochondrial bioenergy could serve to design new therapeutic strategies to work on neurodegenerative diseases in which the functionality of this protein is altered.

"Cells have a series of small specialized structures—cell organelles—that are not independent entities, but they interact, and this helps to regulate their function", notes Professor Francesc Soriano, from the Department of Cell Biology, Physiology and Immunology. "Specifically, the Mfn2 has a mainly mitochondrial localization, but a small portion of the protein is also in the endoplasmic reticulum. In this location, Mfn2 interacts with the mitochondrial Mfn2 and Mfn1 proteins and establishes a bridge between both cell organelles".

In the study, the team confirmed that the problems in the mitochondrial bioenergy in cells with Mfn2 deficiency can be solved with the expression of an artificial Mfn2 protein exclusively localized in the endoplasmic reticulum. "The bioenergetic physiology is restored in the cell, since it allows the establishing of the contacts between those two

organelles, so it favors the journey of the calcium from the endoplasmic reticulum to the mitochondria that activates several enzymes involved in the generation of mitochondrial energy".

Specifically, the team could reverse the defects in the neurite growth in neurons with Mfn2 deficiency thanks to the expression of an artificial Mfn2 protein that joins the endoplasmic reticulum and mitochondria. The study is a first proof of concept of new therapeutic strategies based on the restoration of cellular contacts between the endoplasmic reticulum and the mitochondria in the physiopathology of diseases associated with the Mfn2 protein.

More information: Sergi Casellas-Díaz et al, Mfn2 localization in the ER is necessary for its bioenergetic function and neuritic development, *EMBO reports* (2021). DOI: 10.15252/embr.202051954

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