

Strategy for helping 'tired' cells affected by mitochondrial disease

September 19 2013

Findings published in the latest edition of *Cell* by researchers at the University of Padua and the Centro Nacional de Investigaciones Cardiovasculares have the potential to change the lives of patients with mitochondrial diseases, a group of pathologies characterized by malfunction of mitochondria, the organelles that supply the energy vital for cell function.

The breakthrough concerns a gene called OPA1, which when mutated is responsible for dominant optic atrophy, a hereditary visual disease characterized by a progressive and symmetrical loss vision that becomes apparent early in life.

In an in-depth study of OPA1, groups led by Dr. Luca Scorrano, professor of Biochemistry at the University of Padua, and Dr. José Antonio Enríquez, coordinator of the Tissue Homeostasis and Repair Program at the CNIC, found that this gene has the capacity to act as a "helper" in [cellular metabolism](#), a property that in the future could be exploited for the treatment of [mitochondrial diseases](#), many of which have no known cure.

As Dr. Enríquez explains, "Mitochondria are found in all our cells and regulate important processes such as the production of [usable energy](#) from food-derived molecules and the preparation of cells for division, differentiation or even [cell death](#) if this is appropriate."

Dr. Scorrano adds "For many years our groups worked independently on

the function of mitochondria and diseases linked to their malfunction, with the intention of identifying strategies for the development of specific treatments for mitochondrial diseases and understanding how altered mitochondrial function contributes to more [common diseases](#)."

The two groups joined forces five years ago to try to understand the mitochondrial disease dominant optic atrophy. Patients suffering this visual disease have [mutations](#) in the OPA1 gene. The protein encoded by this gene, which has been characterized by the Italian group over the last several years, regulates the shape of mitochondria. Lack of this protein in dominant optic atrophy patients translates into the progressive death of a type of neuron, the ganglion cells of the retina, which are responsible for transmitting images from the eye to the visual centers of the brain. This loss of neurons, and therefore of sight, is slow but progressive. The disease generally becomes manifest at pre-school age, with varying degrees of seriousness within a single family. Models developed by the Spanish group for the study of mitochondrial function provided novel and appropriate tools for investigating OPA1 function.

According to Enriquez and Scorrano, "What we have demonstrated is that OPA1's task is to regulate the efficiency of respiration, influencing the manner in which the components of the respiratory chain (the complex of proteins that converts energy in nutrients into a form that can be exploited for cellular activities) join together in the internal membrane of mitochondria."

This membrane is like a fluid, folded line which can change shape continually in response to stimuli; the shape of these folds, called cristae, is not random and is determined by the activity of OPA1.

The study demonstrates that by increasing the activity of this protein it is possible to enhance the efficiency of the respiratory chain for production of energy and for cellular growth. The authors propose that

"In the future we may consider the prospect of exploiting this capacity for therapeutic intervention in patients with mitochondrial diseases, to improve metabolism irrespective of the genetic defect responsible for the mitochondrial dysfunction."

"For rare and heterogeneous diseases such as these," Dr. Scorrano explains that "we must discover broad therapeutic approaches which are applicable to various diseases. We are working on this, but it's still too early to speak of a possible treatment."

"Our work marks a major advance in our understanding of the relationship between function and shape in cellular structures" indicates Dr. Enríquez. "The structure of mitochondrial cristae is very peculiar, and surprisingly shows a huge variability in shape between tissues, activity, food regime, pathology, and so on. However, the link between the variable shape of mitochondrial cristae and bioenergetic activity has remained unclear for a long time. This study demonstrates that changing the crista structure induces direct changes in the bioenergetic capacity of the mitochondria through the modulation of superassembly of respiratory complexes."

Provided by Centro Nacional de Investigaciones Cardiovasculares

Citation: Strategy for helping 'tired' cells affected by mitochondrial disease (2013, September 19) retrieved 25 April 2024 from <https://medicalxpress.com/news/2013-09-strategy-cells-affected-mitochondrial-disease.html>

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