Spanish scientists explain how the mitochondrion regulates energy production

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Research news

The study, published recently in the prestigious journal Science Advances, and in which researchers from the University of Granada participated, shows that the mitochondria electron transport chain adjusts its energy efficiency to adapt to the body's needs

This metabolic adaptation mechanism explains mitochondria's ability to modulate to stressful situations, such as those produced by intense physical exercise

Researchers from the University of Granada (UGR) and Spain's National Centre for Cardiovascular Diseases (CNIC) have discovered the molecular mechanism by which mitochondria—the energy source of cells—regulates their functioning to optimally adapt energy production to the needs of the body. The discovery, which was published recently in the journal Science Advances, helps explain how our metabolism is regulated.

The study was led by CNIC researchers Jesús Vázquez and José Antonio Enríquez, with the participation of Jesús Francisco Rodríguez Huertas, Director of the 'José Mataix Verdú' Institute of Nutrition and Food Technology (INYTA) at the Biomedical Research Centre (CIBM) and Professor at the Department of Physiology of the UGR. The results of the study revealed that the electron transport chain (ETC) of the mitochondria adjusts its energy efficiency to adapt to the needs of the body via the regulated association of its macromolecular structures. Furthermore, it demonstrated

that the SCAF1 protein—discovered by this same team in 2016—is a key factor in the regulation of energy metabolism, optimizing the efficiency of the mitochondria when subjected to intense energy demands.

The mitochondria, together with the electron transport chain within them, are in charge of producing the energy that the cell needs, modifying their operation to satisfy the metabolic needs of the body. As the researchers explain, “ETC produces energy from nutritional molecules, such as glucose or fatty acids. In addition, it plays an important role in the synthesis of molecules necessary to maintain the health of cells and the body.”

The mitochondrial respiratory chain is made up of four large multiprotein complexes—CI, CII, CIII, and CIV—which have the ability to structurally reorganize in various ways to perform different functions and adapt to environmental conditions.

In 2016, the CNIC research group participating in the work discovered that the SCAF1 protein forms a bridge between the CIII and CIV complexes, acting as a “molecular switch” that regulates the assembly of these complexes, leading to the formation of super-structures within the ETC (Nature 539, 579–582, 2016. https://doi.org/10.1038/nature20157). However, “we did not know if these structures regulated by SCAF1 play any role in the energy efficiency of the mitochondria and what physiological implications they have for the organism,” notes Jesús Vázquez, Co-director of the research.

The study, which has recently been published in Science Advances, has shown that the formation of specific structures of the SCAF1-regulated electron transport chain not only affects the energy-production efficiency of the mitochondria but also the body’s ability to respond to physiological stress.

“We used mouse models and mouse cell cultures in which the gene for the SCAF1 protein had been removed by genetic engineering, meaning that they were unable to produce it. This allowed us to study how the absence of this protein affected them,” explain the authors.

The researchers used new proteomic techniques developed at the CNIC as well as state-of-the-art genetic, biochemical, and metabolic methods. Using these technologies, “we demonstrated that, in the absence of SCAF1, ETC complexes reorganize at the suboptimal molecular level and, also, that they are less efficient at producing energy,” they note.

Furthermore, the study found that, after being subjected to intense effort, the physical performance of mice that do not express SCAF1 is 30% lower than that of normal mice.

These results explain in molecular terms the results observed in another study recently published in EMBO Reports, which was conducted in collaboration with Nadia Mercader's research group at the University of Bern (Switzerland). In that study, the researchers observed that SCAF1 ablation in the Zebrafish impairs metabolism, growth, and fertility (EMBO Reports. Doi: 10.15252 / embr.202050287).

According to the researchers, these results demonstrate that the physical association between the CIII and CIV complexes, mediated by SCAF1, is decisive for the mitochondria to produce energy optimally. "SCAF1 acts as a regulatory factor that allows the mitochondria to adapt to the available nutritional source of sugars, fats, or proteins," the scientists explain. "This capacity for metabolic adaptation also explains the ability of the mitochondria to adapt to stressful situations, such as those produced by intense physical exercise."

Researchers from the Centre for Biomedical Research in Frailty and Healthy Ageing (CIBERFES) and the Centre for Biomedical Research in Cardiovascular Diseases (CIBERCV) collaborated in the study and received funding from The International Human Frontier Science Program (HFSP RGP0016/2018), Fundació La Marató de TV3, and Fundación Bancaria "La Caixa".

Image caption:

Rafael Casuso, researcher at the INYTA, and Jesús Rodríguez Huertas, Professor of Physiology, Director of the INYTA and of the Department of Physiology of the UGR, and Executive Secretary of the Spanish Society of Physiological Sciences (SECF).

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