Cell: Scientists at the CNIC discover an unexpected involvement of sodium transport in mitochondrial energy generation

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The study, published in *Cell, reveals an essential function of sodium transport in cellular energy generation*

The GENOXPHOS (Functional Genetics of the Oxidative Phosphorylation System) group at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) has discovered a crucial role of sodium in the generation of cellular energy. The study, led by GENOXPHOS group leaderDr. José Antonio Enríquez, also involved the participation of scientists from the Complutense University of Madrid, the Biomedical Research Institute at *Hospital Doce de Octubre*, the David Geffen School of Medicine, UCLA, and the Spanish research networks on frailty and healthy aging (CIBERFES) and cardiovascular disease (CIBERCV).

The study, published in the journal *Cell*, reveals that respiratory complex I, the first enzyme of the mitochondrial electron transport chain, possesses a hitherto unknown sodium transport activity that is crucial for efficient cellular energy production

The discovery of this activity provides a molecular explanation for the origin of the neurodegenerative disease Leber's hereditary optic neuropathy (LHON). First described in 1988, LHON is linked to defects in mitochondrial DNA and is the most frequent mitochondrially inherited disease in the world. The new study shows that the hereditary optic neuropathy in LHON is caused by a specific defect in the transport of sodium and protons by complex I.

According to the chemiosmotic hypothesis, mitochondrial synthesis of ATP—the main source of cellular energy—is driven by an electrochemical gradient of protons across the inner mitochondrial membrane. The hypothesis was first proposed by Dr. Peter Mitchell in 1961 and won him a Nobel Prize in 1978. But since then, the model has remained substantially unchanged. Now, the results of the new study show that this process also involves the transport of sodium ions, a possibility not considered before.

Led by CNIC scientists José Antonio Enríquez and Pablo Hernansanz, the research team used an array of mutants and diverse genetic models to demonstrate that mitochondrial complex I exchanges sodium ions for protons, thus generating a gradient of sodium ions that parallels the proton gradient. This sodium gradient accounts for as much as half of the mitochondrial membrane potential and is essential for ATP production.

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Dr. Enríquez explained that, "Sodium–proton transport activity was lost when we eliminated complex I in mice, but was maintained when we eliminated complex III or complex IV, confirming that sodium–proton transport is directly affected by the lack of complex I function." Through these experiments, the researchers were able to demonstrate that while the two complex I functions (hydrogenase activity and sodium–proton transport) are independent of each other, both are essential for cell function.

Pablo Hernansanz commented that, "Our results demonstrate that mitochondria have a sodium-ion reservoir that is essential for their function and for resisting cellular stress," while José Antonio Enríquez emphasized that the regulation of this mechanism is an essential feature of mammalian biology.

Discussing possible treatments for LHON, José Antonio Enríquez commented that while drugs are available that successfully replicate sodium transport across the inner membrane of isolated mitochondria, clinical use of these drugs is hindered by their toxic secondary effects on sodium transport in the cell membrane. "**The challenge now is to design drugs that act specifically in mitochondria without effecting other parts of the cell**," said Dr. Enríquez.

The researchers also believe that defects in sodium–proton transport may play a role in other, more frequent neurodegenerative diseases such as Parkinson's, in which an involvement of complex I has been detected.

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- *Hernansanz-Agustín P, Morales-Vidal C, Calvo E, Natale P, Martí-Mateos Y, Jaroszewicz SN, Cabrera-Alarcón JL, Acín-Pérez R, López-Montero I, Vázquez J, Enríquez JA. A transmitochondrial sodium gradient controls membrane potential in mammalian mitochondria. **Cell.** 2024 Sep 19, 187: 1-15. doi: 10.1016/j.cell.2024.08.045*