Nature Metabolism: A yeast enzyme helps human cells overcome mitochondrial defects

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A new CNIC-led study shows that a genetic tool derived from baker's yeast enables human cells to manufacture the building blocks of DNA even when their mitochondria fail.

Nucleotide synthesis—the production of the basic components of DNA and RNA—is essential for cell growth and division. In most animal cells, this process depends closely on properly functioning mitochondria, the organelles responsible for respiration and energy production. When mitochondrial respiration fails—a common feature of mitochondrial diseases and several forms of cancer—cells lose the ability to proliferate normally. A new study published in Nature Metabolism now shows that this dependence is not irreversible.

An international team led by José Antonio Enríquez of the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) and the Spanish network for research into frailty and healthy aging (CIBERFES) has experimentally uncoupled nucleotide synthesis from mitochondrial activity using *Sc*URA, a yeast-derived genetic tool now available to the research community that will enable new explorations of cellular metabolism.

The study, which also involved scientists at the University of Cologne (Germany), the University of Valladolid (UVa), and the CSIC–UVa Institute of Biology and Molecular Genetics, sheds new light on the role of mitochondria in rare diseases and cancer.

In complex organisms such as humans, respiration is essential for generating the energy required for life, with the mitochondria in our cells using oxygen to sustain vital cellular processes. By contrast, some organisms—such as the yeast *Saccharomyces cerevisiae*—can survive without oxygen and have evolved alternative metabolic pathways to produce the molecular building blocks required for RNA and DNA synthesis.

Building on this observation, the team identified a yeast enzyme that can sustain nucleotide synthesis independently of mitochondrial respiration. Instead of oxygen, this enzyme uses fumarate, a metabolite derived from nutrients. The team extracted the gene encoding this enzyme, called *Sc* URA, from yeast and inserted it into human cells.

Unlike cells from healthy individuals, the patient-derived cells used in the study cannot grow in standard laboratory conditions because they require extra supplementation with nutrients and DNA precursors. When CNIC researchers introduced *Sc*URA into these diseased cells, they found that the cells were able to grow under normal conditions, just like cells from healthy individuals. "Thanks to the yeast gene, the cells 'learned' to build DNA in a new way," explain the authors.

The results were striking: human cells expressing *Sc*URA continued to produce DNA and RNA even when the mitochondrial respiratory chain was blocked. Unlike the equivalent human enzyme, which is physically linked to the mitochondria, the yeast version works in the cytosol and uses an alternative metabolic pathway.

The team also discovered that *Sc*URA helped cells use their nutrients more efficiently without disrupting other essential cellular functions—an important first step toward the more ambitious goal of improving the lives of people with mitochondrial disorders.

"Mitochondria not only produce energy; they also shape fundamental processes such as DNA synthesis," says lead author José Antonio Enríquez, head of the CNIC GENOXPHOS group. "Our work shows that if we provide a cell with an alternative route to make nucleotides, we can sustain cell proliferation even when mitochondrial respiration fails."

One of the study's most important findings is that *Sc*URA-modified cells can grow without uridine supplementation, a common strategy used in laboratories to compensate for mitochondrial defects.

Moreover, the new approach restores cell proliferation across different experimental models of

mitochondrial diseases, including those caused by severe mutations in essential respiratory chain complexes. For first author Andrea Curtabbi (CNIC), “this tool allows us, for the first time, to clearly separate the direct effects of mitochondrial dysfunction on nucleotide synthesis from other secondary metabolic changes.”

Mitochondrial diseases are severe and often untreatable, and in the laboratory cells with impaired mitochondrial respiration require external supplements to proliferate. However, when the researchers inserted *Sc*URA into these cells, they proliferated under standard conditions in the same way as healthy cells.

The study also shows that this imported enzyme boosts the efficiency of nutrient use without altering other essential cellular functions, making *Sc*URA a highly valuable experimental tool. The authors further highlight its potential for clarifying mitochondrial contributions to rare diseases and cancer. “Identifying which metabolic processes become limiting when mitochondrial respiration fails is crucial for designing precise therapeutic strategies,” concludes Enríquez.

In future work, the team plans to expand their findings to other disease models and optimize this approach for preclinical research.

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