Experimental therapy may offer hope for rare genetic disorders

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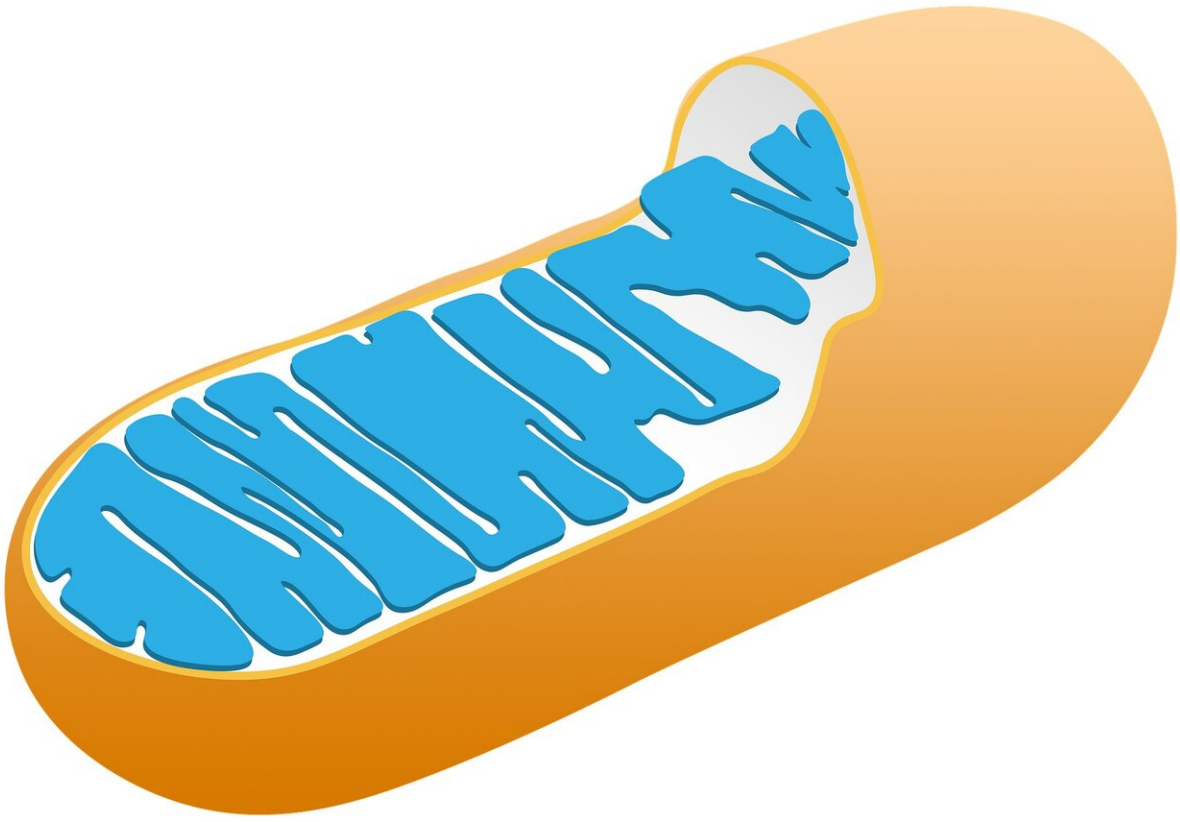

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Researchers at Massachusetts General Hospital (MGH) have developed a new way to alleviate problems caused by dysfunctional mitochondria, which are the "powerhouses" that produce energy in cells. Their discovery, reported in the journal *Nature Biotechnology* on January 13, could lead to a new treatment for rare diseases caused by "broken" mitochondria, but could also be used to develop novel therapies for more common age-associated disorders.

All cells have mitochondria. "Mitochondria take electrons from the food we eat and transfer them to oxygen," explains Vamsi Mootha, MD, investigator in the Department of Molecular Biology at MGH, and senior author of the Nature Biotechnology paper. Mootha compares this process to a river flowing down a mountain, with water wheels that harness the flow to produce energy.

However, mitochondrial disorders act like a dam by blocking this smooth flow and causing a pileup of electrons, known as a redox imbalance, and stalling vital chemical reactions inside the cell. "We think toxicity is coming from the fact that the 'waterwheel' is no longer spinning," says Mootha. The excess electrons eventually spill into blood circulation in the form of lactate, a molecule that serves as a marker for the disease occurring inside the cells.

Malfunctioning mitochondria cause more than 300 rare genetic disorders, such as Leigh syndrome (a crippling neurological disease that can present early in infancy) and MELAS (which causes muscle weakness, diabetes, and strokes, with onset usually before age 40). However, a gradual fall-off in mitochondrial function also occurs in Parkinson's disease and other more common disorders. "Even the aging

process itself, absent disease, is associated with a decline in mitochondrial activity," says Mootha.

To address the problem, Mootha and his colleagues created a synthetic enzyme (called LOXCAT) by combining two bacterial proteins, lactate oxidase (LOX) and catalase (CAT). His team added LOXCAT to a medium of cultured human cells with defective mitochondria and found that the artificial enzyme converts lactate to pyruvate, which enters cells and picks up electrons, relieving the pileup. Pyruvate in turn converts to lactate, which is released from the cell. LOXCAT reconverts the lactate to pyruvate, which starts the process anew, creating a cycle.

"Our new therapeutic directly targets circulating lactate as a means of safely dissipating excess electrons. Redox balance is restored and flow inside the cell resumes," says Mootha. "What's conceptually new here is that our enzyme doesn't have to enter the cell—it operates on the incoming and exiting chemicals to benefit the cell's inner workings."

Mootha notes that more engineering remains to be done before LOXCAT is ready for testing in humans. But he feels this research, which was funded by the Marriott Foundation, could have a profound impact. "Right now, we have very few, if any, ways of dealing with the consequences of mitochondrial dysfunction," says Mootha. "This novel approach will potentially help a lot of diverse genetic conditions whose common final endpoint is redox imbalance."

The lead author of the Nature Biotechnology paper is Anupam Patgiri, Ph.D., a research fellow in the Department of Molecular Biology at MGH. Senior author Vamsi Mootha, MD, directs the Mootha Laboratory, which is based at MGH's Department of Molecular Biology. He is also a professor of Systems Biology at Harvard Medical School, an investigator at the Howard Hughes Medical Institute, and a member of the Broad Institute, in Cambridge, Massachusetts.

More information: An engineered enzyme that targets circulating lactate to alleviate intracellular NADH:NAD+ imbalance, *Nature Biotechnology* (2020). DOI: 10.1038/s41587-019-0377-7 , nature.com/articles/s41587-019-0377-7

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