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Scientists find potential target for treating mitochondrial disorders

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Mitochondria, long known as "cellular power plants" for their generation of the key energy source adenosine triphosphate (ATP), are essential for proper cellular functions. Mitochondrial defects are often observed in a variety of diseases, including cancer, Alzheimer's disease, and Parkinson's disease, and are the hallmarks of a number of genetic mitochondrial disorders whose manifestations range from muscle weakness to organ failure. Despite a fairly strong understanding of the pathology of such genetic mitochondrial disorders, efforts to treat them have been largely ineffective.

But now, graduate student Walter Chen and postdoctoral researcher Kivanc Birsoy, both part of Whitehead Institute Member David Sabatini's lab, have unraveled how to rescue cells suffering from mitochondrial dysfunction, a finding that may lead to new therapies for this condition.

To find genetic mutations that would rescue the cells, Chen and Birsoy mimicked mitochondrial dysfunction in a haploid genetic system developed by former Whitehead Fellow Thijn Brummelkamp. After suppressing mitochondrial function using the drug antimycin, Chen and Birsoy saw that cells with mutations inactivating the gene ATPIF1 were protected against loss of mitochondrial function.

ATPIF1 is part of a backup system to save starving cells. When cells are deprived of oxygen and sugars, a mitochondrial complex that usually produces ATP, called ATP synthase, switches to consuming it, a state

that can be harmful to an already starving cell. ATPIF1 interacts with ATP synthase to shut it down and prevent it from consuming the mitochondrion's dwindling ATP supply but, in the process, also worsens the mitochondrion's membrane potential

"In these diseases of mitochondrial dysfunction, in a sense, it's a false starvation situation for the cell—there are plenty of nutrients, but because there's a block in the mitochondria's normal function, the mitochondria behave as if there's not enough oxygen," says Chen, who with Birsoy, authored a paper in the journal *Cell Reports* describing this work. "So in these situations, activation of ATPIF1 is not good, because there are still many nutrients around to provide ATP. Instead, blocking ATPIF1 is therapeutic because it allows for maintenance of the membrane potential."

Liver cells are frequently affected in patients with severe mitochondrial disease, so Chen and Birsoy tested the effects of mitochondrial dysfunction in the liver cells of control mice and mice with ATPIF1 genetically knocked out. Again, the liver cells with suppressed ATPIF1 function dealt better with mitochondrial dysfunction than liver cells with normal ATPIF1 activity.

"It's very simple—if you get rid of ATPIF1, you survive in the presence of mitochondrial dysfunction," says Birsoy. "From what we see so far, there are no major side effects from blocking ATPIF1 in mice."

For Chen and Birsoy, the next step in this line of research is to test the effects of ATPIF1 suppression in mouse models of mitochondrial dysfunction. Then they will try to identify therapeutics that effectively block ATPIF1 function.

More information: "Inhibition of ATPIF1 Ameliorates Severe Mitochondrial Respiratory Chain Dysfunction in Mammalian Cells" *Cell*

Reports, April 10, 2014.

Provided by Whitehead Institute for Biomedical Research