Molecular link found between high glucose, metabolic disease

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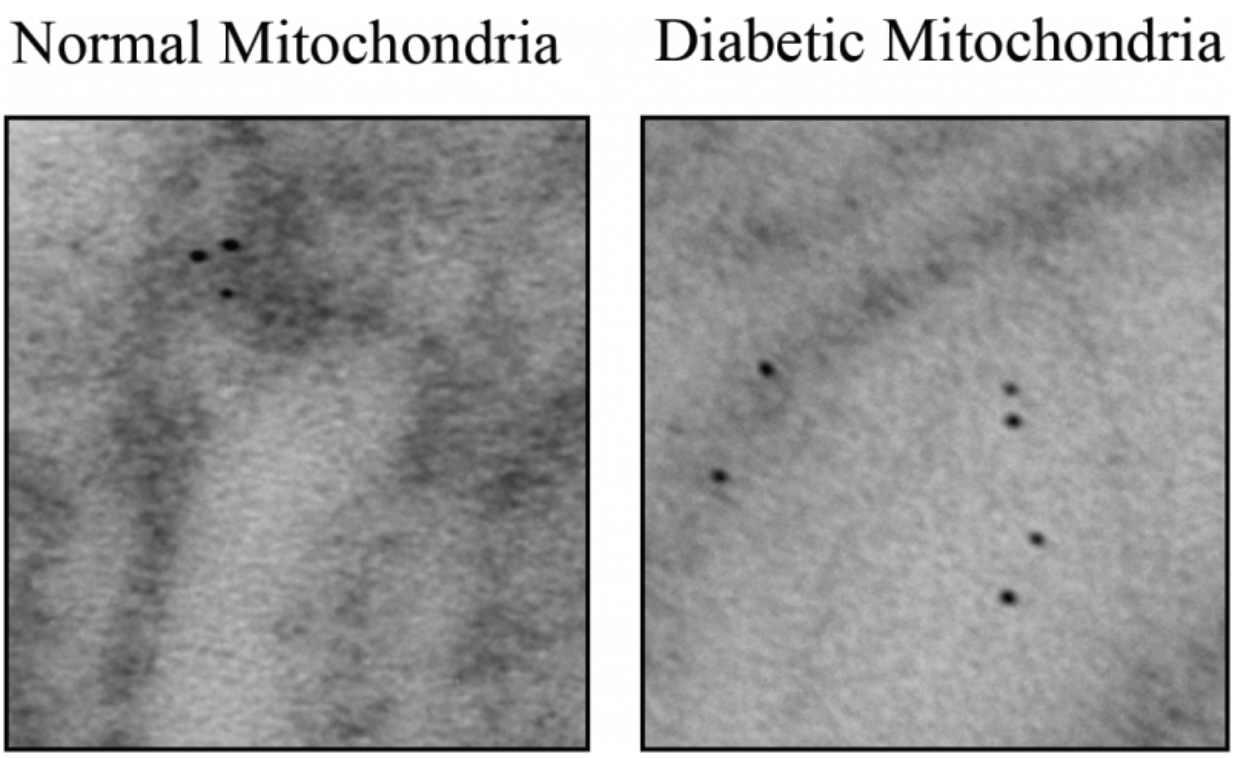

An electron microscope image shows dark-stained O-GlcNAc transferase localized to one complex in the mitochondrial membrane, left, and scattered to the inside of the mitochondria, right. Credit: Partha Banerjee/Johns Hopkins Medicine

Scientists at Johns Hopkins say they've discovered a cause-and-effect link between chronic high blood sugar and disruption of mitochondria,

the powerhouses that create the metabolic energy that runs living cells. The discovery, reported online in *Proceedings of the National Academy of Sciences* on April 27, sheds light on a long-hidden connection and, they say, could eventually lead to new ways of preventing and treating diabetes.

"Sugar itself isn't toxic, so it's been a mystery why high blood sugar can have such a profound effect on the body," says Gerald Hart, Ph.D. , director of the Johns Hopkins University School of Medicine's Department of Biological Chemistry. "The answer seems to be that high blood sugar disrupts the activity of a molecule that is involved in numerous processes within the cell."

Previous experiments by other research groups had shown that the high blood sugar of untreated diabetes alters the activity of mitochondria, compartments that process nutrients into useable energy for cells. To find out why, postdoctoral fellow Partha Banerjee, Ph.D., compared the enzymes in mitochondria from the hearts of rats with diabetes to those from healthy rat hearts. He looked for differences in levels of two enzymes that add and remove a molecule called O-GlcNAc to proteins. Hart's research group has for 30 years studied cells' use of O-GlcNAc to control how nutrients and energy are processed.

Banerjee found that levels of one enzyme, O-GlcNAc transferase, that adds O-GlcNAc to proteins was higher in the diabetic rat mitochondria, while levels of an enzyme that removes O-GlcNAc, O-GlcNAcase, were down.

"We expected the enzyme levels to be different in diabetes, but we didn't expect the large difference we saw," Banerjee says. He and his colleagues say they also found that the location of one of the enzymes within the mitochondria was different in the diabetic mice. Producing energy requires an intricate interplay between enzyme complexes

embedded in mitochondrial membranes, each with a distinctive role. O-GlcNAc transferase is normally found in one of these complexes, but in the diabetic mice, much of it had migrated to the inside of the mitochondria, Banerjee says.

The net effect of the changes in O-GlcNAc-related activity, Hart says, is to make energy production in the mitochondria less efficient so that the mitochondria begin to produce more heat and damaging molecules as byproducts of the process. The liver then kicks off an antioxidant process for neutralizing so-called free radicals, which involves making more glucose, increasing blood sugar further.

Finding a medication that normalizes activity of the O-GlcNAc enzymes, he says, could be an effective way to prevent or treat diabetes.

More information: Diabetes-associated dysregulation of O-GlcNAcylation in rat cardiac mitochondria, Partha S. Banerjee, DOI: 10.1073/pnas.1424017112

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