Team uncovers new functions of mitochondrial fusion

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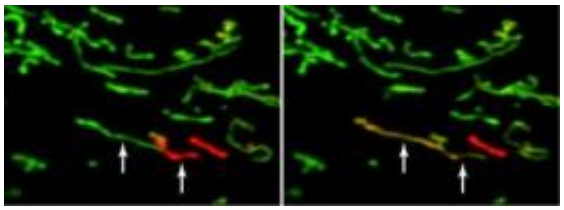

In the first panel, two separate mitochondria are labeled green and red (indicated by arrows). Ten seconds later (see second panel), these two mitochondria have fused into one, as shown by the diffusion of the two colors throughout the merged mitochondrion. Credit: Caltech/Anh Pham

A typical human cell contains hundreds of mitochondria—energy-producing organelles—that continually fuse and divide. Relatively little is known, however, about why mitochondria undergo this behavior.

In a paper published in the April 16 issue of the journal *Cell*, a team of researchers—led by scientists at the California Institute of Technology (Caltech)—have taken steps toward a fuller understanding of this process by revealing just what happens to the organelle, its DNA (mtDNA), and its energy-producing ability when mitochondrial fusion fails. In the process, the researchers show that fusion (the merging of two mitochondria) is "highly protective, allowing the mitochondria to tolerate very high loads of mitochondrial DNA mutations," says David Chan, associate professor of biology at Caltech and a Howard Hughes Medical Institute (HHMI) investigator.

These findings, Chan adds, help to shed light on the pathogenesis behind human mitochondrial encephalomyopathies—a class of neuromuscular diseases caused by mutations in mtDNA. In these diseases, muscle weakness occurs due to the loss of energy production by mitochondria.

When first discovered, mitochondrial fusion was thought simply to control the shape of mitochondria. And indeed, Chan says, that is at least partially the case. "If you don't have fusion to balance division, the mitochondria get smaller and smaller as they divide," he explains.

But what hadn't been appreciated in the past, he says—and what the research described in the Cell paper makes clear—is that these smaller mitochondria undergo much more than a cosmetic change. "We've showed that in mammalian cells, there are physiological consequences if there's no mitochondrial fusion," says Chan.

To show just what happens, the team created mice with defects in two proteins known as mitofusins—mfn1 and mfn2—which are located on the surface of the mitochondria and are essential to the process of fusion. "We were able to specifically delete these mitofusins in skeletal muscle," Chan explains.

As it turns out, when fusion is blocked, not only are the mitochondria smaller, but the mtDNA levels in the mitochondria drop precipitously. As for the mice themselves? While they are born looking relatively normal, over the next couple of months they show signs that something is going wrong. Their growth is severely stunted and they die by 7-8 weeks of age, just at the onset of adulthood.

The mtDNA that remains in these unfused mitochondria "has a higher accumulation of point mutations and deletions," says Chan. In other words, without fusion, the mtDNA contains more mistakes, suggesting that fusion is "necessary for mtDNA stability."

This work may be important to our understanding of how and why human mitochondrial encephalomyopathies come to pass. Scientists have noted that most cells have a remarkably high tolerance for the mtDNA mutations that cause

these conditions; in fact, somewhere between 60 and 90 percent of mtDNA has to carry the mutation before symptoms will begin to appear in a person with the mtDNA mutation. "Cells can tolerate a very high load of mtDNA mutations," Chan notes.

Why? Possibly because each cell carries so many copies of mtDNA that the "normal" versions are able to make up for the miscues of the mutated versions—but only if the mitochondria are able to fuse and combine their contents from time to time.

Chan and colleagues showed this to be the case in another set of experiments, in which they looked at a mouse model known to carry a high number of mtDNA mutations. Due to these mtDNA mutations, Chan explains, the mouse line has a lifespan less than half that of a normal mouse.

Still, it could be much worse—as Chan and colleagues showed when they tweaked the mouse model so that its mitochondria could no longer fuse. "When we added the mfn1 mutation into this model, we found that the mice died at birth instead of surviving to one year of age," he says. These results suggest that mitochondrial fusion is highly protective in cells carrying mtDNA mutations, as would be the case in encephalomyopathies.

Now that they've identified the problems that lack of fusion cause, the team plans to address the mechanisms by which these issues arise. "Why is there less mtDNA?" asks Chan. "Why is there less fidelity in the mtDNA genome? That's what we're going to study now."

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