New mechanism underlying organelle communication revealed in brown fat cells

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In recent years, brown fat has garnered increasing attention as the so-called good fat that can protect against obesity and associated health risks, like cardiovascular disease and diabetes. Brown fat is located in

small pockets throughout the body and helps maintain body temperature in cold environments. It gets its color from high amounts of iron-containing mitochondria, unlike the standard white fat linked to obesity.

A team led by Ling Qi, Ph.D., professor of molecular & integrative physiology and internal medicine at U-M Medical School has been studying how mitochondria, the power plant of the cell, and another cellular structure called the endoplasmic reticulum (ER), which is involved in the production of proteins and lipids, interact inside brown fat cells.

In particular, they've studied the role of a protein complex involved in a process called ER-associated protein degradation, or ERAD. Simply put, ERAD is the process of removing and destroying misfolded proteins, like taking out the trash out of the ER.

"Everyone thought that ERAD was just part of the general cellular response when cells are undergoing ER stress," says Qi. "We've shown over the past six years that it plays a fundamental role in health and disease."

In a new study, published as a Research Article in *Science*, Qi along with first authors Zhangsen Zhou, Ph.D., Mauricio Torres, Ph.D., and their colleagues demonstrate how an ERAD protein complex affects the proper function of mitochondria.

Typically, the ER and mitochondria have ongoing interaction at touch points called mitochondria-associated membranes. These points of contact, mark areas for mitochondria to divide for the production of new mitochondria and for the exchange of other molecules such as lipids and calcium. The ER forms tubules that surround the mitochondria to get them ready for division.

Using state-of-the-art 3-D imaging, the researchers discovered what happens to mitochondria in brown fat that are missing part of an ERAD protein complex, called Sel1L-Hrd1, when exposed to cold.

"When you delete this complex in brown adipocytes, the mitochondria become elongated and enlarged," says Qi. The 3-D image enabled them to view a previously unrecognized interaction between the mitochondria and the ER, with the mitochondria wrapping in a U-shape around the ER tubules.

When the mice were placed in a cold environment, the ends of the outer membrane of the mitochondria folded back on itself, eventually fusing and completely enveloping the ER tubules. The result, says Qi, are abnormally large, misshapen, dysfunctional mitochondria.

"We showed that these mitochondria don't function normally and the mice become cold sensitive, their body temperature dropping very quickly," says Qi. In other words, without this ERAD protein complex, the brown fat is not being used to generate heat. Under a microscope, this dysfunctional brown fat had larger droplets of lipids than brown fat from mice with the protein complex intact. "This is highly unexpected. The results here fundamentally change our understanding of ER-mitochondrial communication and further demonstrate the importance of an ER degradation complex in cell biology."

More information: Zhangsen Zhou et al, Endoplasmic reticulum–associated degradation regulates mitochondrial dynamics in brown adipocytes, *Science* (2020). DOI: 10.1126/science.aay2494

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