

## Protein degradation regulates contact between organelles

By Yusi Fu, Patricia Rohs, and Yue Zhou

Preview on Zhou, Z. *et al.* Endoplasmic reticulum–associated degradation regulates mitochondrial dynamics in brown adipocytes. *Science* **368**, 54–60 (2020)<sup>1</sup>

The COVID-19 pandemic shows us that nobody in the world is an isolated island. Just as countries and regions in the world are highly connected and function as a network, compartments in an individual cell also rely on crosstalk to be fully functional. Organelles, either membrane-bound or phase separated compartments in eukaryotic cells, are self-separated to maintain a suitable local environment for specialized chemical reactions, such as energy production or storage, lipid oxidation, lipid or protein hydrolysis, protein synthesis or modification, or cargo delivery. At the same time, no organelles can function without intercommunication, especially upon environmental challenges. It is crucial for organelles to adapt to environmental changes for the cell to survive, and that is when organelle crosstalk comes under the spotlight.

The first discovered inter-organelle communication, the close contact between endoplasmic reticulum (ER) and mitochondria, was first observed in the 1950's<sup>2</sup>, and it was not until the 1990's that people start to realize that this close contact has important functions to the cell<sup>3</sup>. Besides enabling metabolite transportation<sup>4</sup>, the tethering between ER and mitochondria is also essential for mitochondrial fission<sup>5</sup>. Mitochondrial fission and fusion are crucial for cellular functions such as thermogenesis in brown adipocytes, and the dysfunction of mitochondrial dynamics can lead to metabolic diseases.

In this recent publication, *Zhou et al.* revealed a new mechanism by which the ER regulates mitochondrial dynamics. They determined that the ER-associated protein degradation (ERAD) complex Sel1L-Hrd1 is required for the maintenance of mitochondrial function and morphology in brown adipocytes under cold challenges. Surprisingly, the mitochondrial defects observed in ERAD-deficient mice are not caused by the accumulation of misfolded mitochondrial proteins. Instead, ERAD controls levels of the protein SigmaR1, which localizes to mitochondria-associated membranes (MAMs) within ER. In ERAD-deficient mice, SigmaR1 accumulates and forms aberrant ER-mitochondria contacts, resulting in impaired mitochondrial function and dynamics.

This study originated with the serendipitous observation of abnormal mitochondria in Sel1L-depleted primary brown preadipocytes, suggesting that Sel1L-mediated ERAD may regulate mitochondrial dynamics. The authors generated brown adipocyte-specific Sel1L-deficient mice, which grew normally and showed no difference in mitochondrial morphology at 22°C. However, within hours of cold exposure, mitochondria in the brown adipose tissue became large and branched, with closer contact to the ER, and sometimes even had perforating ER tubules. Similar results were seen in mice deficient for the ERAD protein Hrd1. Purified “megamitochondria” from Sel1L-deficient brown adipose tissue had a reduced oxygen consumption rate, and Sel1L<sup>-/-</sup> adipocytes had an altered metabolic profile consistent with mitochondrial dysfunction. ERAD-deficient mice were unable to maintain their core body temperature upon cold exposure, perhaps due to defects in lipid mobilization.

One mechanism by which ERAD could regulate mitochondrial function is by degrading mitochondrial proteins. However, the levels of all tested mitochondrial proteins were unaffected in Sel1L-deficient brown adipose tissue. Instead, the strange mitochondrial morphologies may be due to reduced phosphorylation of the fission factor Drp1, failure to process the fusion factor Opa1 to its shorter form, and increased oligomerization of Mitofusin 2 in Sel1L<sup>-/-</sup> brown adipocytes. The authors next tested the hypothesis that ERAD regulates mitochondrial function via MAMs of the ER, which are indispensable for mitochondrial DNA synthesis and fission. They found that the MAM protein SigmaR1 had increased abundance in ERAD-deficient brown adipose tissue on the protein level but not the transcriptional level. Deletion of SigmaR1 rescued mitochondrial morphology and reduced ER-mitochondrial contacts, further validating SigmaR1 as the linker between ERAD and mitochondrial dynamics. Collectively, these data show that ERAD regulates the function and dynamics of mitochondria by degrading the MAM protein SigmaR1.

While this and other studies have linked SigmaR1 to mitochondrial function, its mechanism of action is unclear<sup>6,7</sup>. The observation that brown adipocytes of ERAD-deficient mice contain “megamitochondria” suggests that the excess SigmaR1 either inhibits mitochondrial fission or promotes mitochondrial fusion. ER-mitochondrial contacts are known to stimulate mitochondrial fission<sup>5</sup>, but SigmaR1 was not observed to interact with known mitochondrial fission factors. It is also unclear whether the SigmaR1 that accumulates in ERAD-deficient mice is functional, or whether the observed phenotypes are caused by dominant-negative activity of misfolded SigmaR1. Finally, the importance of SigmaR1 varies depending on the tissue and condition. Although SigmaR1 constitutively accumulates in the adipocytes of ERAD-deficient mice, mitochondrial defects only occur upon acute cold challenge. Other studies have shown that loss of SigmaR1 affects mitochondria in motor neurons but not sensory neurons<sup>6</sup>. Further exploration of SigmaR1 function and interaction partners may explain this tissue specificity.

This study was an important step forward in understanding how specific ER proteins affect mitochondrial function. A small number of ER proteins are known to interact with mitochondria to facilitate tethering and calcium exchange<sup>8</sup>. Here, *Zhou et al* reveal that ERAD controls the abundance of at least one protein found at ER-mitochondrial contact sites, and show that this regulation is critical for mitochondrial function in brown adipose tissue. Future studies will address what signals or adaptor proteins are required for ER-associated degradation of SigmaR1, and uncover the mechanisms connecting SigmaR1 levels to mitochondrial function.

1. Zhou, Z. *et al*. Endoplasmic reticulum–associated degradation regulates mitochondrial dynamics in brown adipocytes. *Science* **368**, 54–60 (2020).
2. Bernhard, W. & Rouiller, C. Close topographical relationship between mitochondria and ergastoplasm of liver cells in a definite phase of cellular activity. *J. Biophys. Biochem. Cytol.* **2**, 73–78 (1956).
3. Vance, J. E. Phospholipid synthesis in a membrane fraction associated with mitochondria. *J. Biol. Chem.* **265**, 7248–7256 (1990).
4. Shai, N. *et al*. Systematic mapping of contact sites reveals tethers and a function for the peroxisome-mitochondria contact. *Nat. Commun.* **9**, (2018).

5. Friedman, J. R. *et al.* ER Tubules Mark Sites of Mitochondrial Division. *Science* **334**, 358–362 (2011).
6. Bernard-Marissal, N., Médard, J.-J., Azzedine, H. & Chrast, R. Dysfunction in endoplasmic reticulum-mitochondria crosstalk underlies SIGMAR1 loss of function mediated motor neuron degeneration. *Brain J. Neurol.* **138**, 875–890 (2015).
7. Gregianin, E. *et al.* Loss-of-function mutations in the SIGMAR1 gene cause distal hereditary motor neuropathy by impairing ER-mitochondria tethering and Ca<sup>2+</sup> signalling. *Hum. Mol. Genet.* **25**, 3741–3753 (2016).
8. Wu, H., Carvalho, P. & Voeltz, G. K. Here, there, and everywhere: The importance of ER membrane contact sites. *Science* **361**, eaan5835 (2018).