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LIPID METABOLISM

Fatty acids on the move

> fatty acids destined for oxidative respiration are released from lipid droplets by lipolysis

During starvation, fatty acids are trafficked from lipid droplets to mitochondria, where they are oxidized to drive oxidative respiration; however, a mechanistic understanding of this journey was lacking. Lippincott-Schwartz and colleagues now reveal that fatty acids destined for oxidative respiration are released from lipid droplets by lipolysis; lipid droplets must be close to fused mitochondria for fatty acid–mitochondria movement.

The authors developed a pulse-chase assay to track fatty acids in starved mouse embryonic fibroblasts (MEFs) and, using spinning-disk confocal microscopy, they observed that fatty acids redistribute from lipid droplets to mitochondria upon nutrient starvation. They next assessed whether fatty acids are released from lipid droplets by lipases or lipophagy (a form of autophagy specific for lipid droplets). The knockdown of adipose triglyceride lipase (ATGL) — a cytoplasmic neutral lipase — in starved MEFs, or the pharmacological inhibition of lipase function, reduced the redistribution of fatty acids from lipid droplets to mitochondria and decreased the mitochondrial oxygen consumption rate (mtOCR). By contrast, the genetic or pharmacological inhibition of autophagosome formation (and thus lipophagy) had no effect on fatty acid trafficking or mtOCR. Thus, lipolysis, and not lipophagy, releases fatty acids from lipid droplets in response to starvation.

Interestingly, the authors found a role for macroautophagy (non-specific bulk autophagy) in the shuttling of fatty acids in starved MEFs. Lipid droplets grew in size and number in wild-type but not macroautophagy-deficient cells. By labelling and monitoring phosphatidylcholine (a major constituent of cell membranes) the authors were able to conclude that cellular membranes are shuttled to lysosomes by macroautophagy, where they are broken down to release fatty acids that can associate with lipid droplets; this ensures a sufficient supply of lipid droplets during starvation.

But, how do fatty acids released from lipid droplets by lipolysis enter mitochondria? The authors observed that lipid droplets in starved MEFs were closely associated with mitochondria, which suggests that fatty acids might traffic directly between these organelles. Mitochondria were also found to be highly fused and to contain a homogenous distribution of fatty acids. As this even distribution was lost in MEFs deficient in mitofusin 1 (MFN1) or OPA1 — the major mitochondrial fusion proteins — mitochondrial fusion seems to be necessary for this phenomenon. Indeed, unlike control cells, MFN1-null cells were unable to sustain mtOCR under starvation and, interestingly, nutrient-depleted MFN1- and OPA1-deficient cells had three times more lipid droplets than control cells, suggesting that fatty acids that cannot be efficiently taken up by fusion-deficient mitochondria re-associate with lipid droplets.

In short, this study shows that, during starvation, fatty acids are released from lipid droplets by lipolysis and taken up by fused mitochondria to support oxidative respiration.

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ORIGINAL RESEARCH PAPER Rambold, A. S., Cohen, S. & Lippincott-Schwartz, J. Fatty acid trafficking in starved cells: regulation by lipid droplet lipolysis, autophagy, and mitochondrial fusion dynamics. *Dev. Cell* http://dx.doi.org/10.1016/j.devcel.2015.01.029 (2015)

FURTHER READING Thiam, A. R., Farese Jr, R. V. & Walther, T. C. The biophysics and cell biology of lipid droplets. *Nature Reviews Mol. Cell Biol.* **14**, 775–786 (2013)