

 AUTOPHAGY

From one membrane to another

During starvation-induced autophagy, double-membrane structures called autophagosomes engulf cytosol or organelles and deliver them to lysosomes to be degraded and released as nutrients. The origin of autophagosome membranes was unclear, but Hailey *et al.* present evidence suggesting that the mitochondrial outer membrane contributes to their biogenesis during starvation.

To identify membranes that contribute to autophagosomes, the authors expressed fluorescently labelled proteins targeted to different organelles in a normal rat kidney (NRK) cell line expressing cyan fluorescent protein (CFP) fused to the late autophagosome marker LC3 (also known as MAP1LC3B). Only a mitochondrion-targeted isoform of cytochrome b5, which specifically labels the mitochondrial outer membrane, extensively overlapped with CFP-LC3-labelled autophagosomes. This occurred specifically during starvation-induced autophagy and was

not due to mitophagy (the selective autophagic capture of mitochondria), as inner mitochondrial membrane and mitochondrial matrix markers did not overlap with starvation-induced CFP-LC3-positive structures.

So, could the mitochondrial outer membrane be used in autophagosome formation during starvation? The authors visualized NRK cells expressing Mito-red fluorescent protein (which localizes to mitochondria) and fluorescently tagged autophagosome protein markers (LC3 or autophagy protein 5 (ATG5)) under starvation and observed that regions of LC3 and ATG5 staining first appear associated with mitochondria. Furthermore, transmission electron microscopy showed that autophagosomes appear adjacent to mitochondria. Finally, photobleaching of fluorescently labelled mitochondrial membranes also depleted signal from associated autophagosomes, indicating that mitochondria and autophagosomes share membrane, at least transiently.

Autophagosomal membranes should contain lipid components of mitochondrial outer membranes if they originate from them. The lipid phosphatidylserine is transferred from the endoplasmic reticulum (ER) to mitochondria, where it is converted to phosphatidylethanolamine, which is conjugated to LC3 in autophagosome membranes. A fluorescently labelled analogue of phosphatidylserine appeared on starvation-induced autophagosomes, and perturbing ER-mitochondrion contacts to block lipid transfer prevented the formation of starvation-induced autophagosomes. This supports the idea that autophagosome membrane lipids originate from mitochondria in starving cells.

In short, this study suggests that the mitochondrial outer membrane is at least one source of autophagosome membranes during starvation.

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ORIGINAL RESEARCH PAPER Hailey, D. W. *et al.*
Mitochondria supply membranes for autophagosome biogenesis during starvation. *Cell* **141**, 656–667 (2010)

FURTHER READING Nakatogawa, H. *et al.*
Dynamics and diversity in autophagy mechanisms: lessons from yeast. *Nature Rev. Mol. Cell Biol.* **10**, 458–467 (2009)

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mitochondrial outer membrane contributes to [autophagosome] biogenesis during starvation
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