*Nature Reviews Molecular Cell Biology* | AOP, published online 14 October 2009; doi:10.1038/nrm2790

AUTOPHAGY

# Autophagy takes an alternative route

Autophagy-related protein 5 (ATG5) and ATG7 are thought to be essential for mammalian autophagy (also known as macroautophagy) — the lysosomal breakdown of organelles, proteins and other components of the cytoplasm to sustain metabolism during starvation and metabolic stress. Now, a study in *Nature* has uncovered an ATG5- and ATG7-independent pathway that controls autophagy.

Nishida *et al.* observed autophagic structures, such as autophagosomes (double membrane-bound vesicles that sequester materials to be degraded and deliver them to lysosomes), in *Atg5*$^{-/-}$ and in *Atg7*$^{-/-}$ mouse embryonic fibroblasts (MEFs) that were treated with etoposide (a cellular stress-inducing agent) or starved. This suggests that an ATG5- and ATG7-independent autophagy system exists.

As some markers of the 'conventional' autophagy pathway were not seen in *Atg5*$^{-/-}$ or *Atg7*$^{-/-}$ MEFs undergoing this process, the authors sought to identify the mechanism of ATG5- and ATG7-independent autophagy. Gene expression analysis and silencing experiments in etoposide-treated and untreated *Atg5*$^{-/-}$ MEFs showed that the alternative autophagy pathway requires some components of the conventional autophagy pathway, such as UNC51-like kinase 1 and the phosphoinositide 3-kinase complexes (which act upstream to initiate autophagy), but not other components, such as proteins in the ubiquitin-like protein conjugation system (which is downstream in the pathway). Furthermore, RAB9, which is involved in trafficking from late endosomes to the *trans*-Golgi, is crucial for the formation of autophagosomes in the ATG5-independent route, but not during conventional autophagy.

> “an ATG5- and ATG7-independent pathway that controls autophagy.”

Next, the authors found that autophagic vacuoles are present in several *Atg5*$^{-/-}$ embryonic tissues. Notably, the mitochondria of maturing erythrocytes are still digested in the vacuoles of *Atg5*$^{-/-}$ mice, thereby suggesting that the alternative autophagy pathway is involved in the elimination of mitochondria during erythroid terminal differentiation.

Together these results show that mammalian autophagy can occur through a canonical ATG5- and ATG7-dependent pathway and through an alternative ATG5- and ATG7-independent pathway. Whether these two pathways have different physiological roles and/or are activated by different stimuli in different cell types remains to be investigated.

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**ORIGINAL RESEARCH PAPER** Nishida, Y. *et al.* Discovery of Atg5/Atg7-independent alternative macroautophagy. *Nature* **461**, 654–658 (2009)
**FURTHER READING** Nakatogawa, H. *et al.* Dynamics and diversity in autophagy mechanisms: lessons from yeast. *Nature Rev. Mol. Cell Biol.* **10**, 458–467 (2009) | Kroemer, G. & Levine, B. Autophagic cell death: the story of a misnomer. *Nature Rev. Mol. Cell Biol.* **9**, 1004–1010 (2008)