Nature Reviews Molecular Cell Biology | AOP, published online 7 August 2013; doi:10.1038/nrm3646

AUTOPHAGY

Atg independence in the midgut

> Uba1 seems to have a role in autophagy specifically during this developmental process

Autophagy usually depends on a discrete set of autophagy-related (ATG) proteins that function in a specific order. However, some reports show that it can occur independently of certain ATG proteins. Chang *et al.* provide further evidence for this by showing that autophagy that reduces cell size during development of the *Drosophila melanogaster* intestine is independent of Atg7 and Atg3.

The intestine shortens during the transition from the larval to the pupal stage in *D. melanogaster*, and this shortening involves autophagy.

PhotoDisc/Getty Images

To investigate this further, the authors assessed the morphology of midgut cells following depletion of Atg2 or Atg18 — proteins that are required for autophagosome formation. Wild-type cells, but not those depleted of Atg2 or Atg18, were smaller following the induction of autophagy. The targeted knockdown of Atg18 in clones of cells showed that autophagy reduces midgut cell size in a cell-autonomous manner.

Further experiments demonstrated that other key Atg proteins, including the ubiquitin-like protein Atg8a, were also required for the autophagy-dependent reduction in midgut cell size. Surprisingly, however, knockdown of the E1-activating enzyme Atg7, which is required for Atg8a lipidation, did not prevent this. Thus, autophagy in the degenerating *D. melanogaster* midgut is Atg7 independent. Instead, the authors found that ubiquitin-activating enzyme 1 (Uba1) was required for reduced midgut cell size and midgut cell autophagy. Uba1 seems to have a role in autophagy specifically during this developmental process as it is not required for starvation-induced autophagy in the midgut or fat body of *D. melanogaster*.

Further experiments showed that Uba1 could not activate Atg8a and therefore did not 'substitute' for Atg7. Thus, the authors questioned the involvement of Atg8a lipidation in autophagy occurring in their model. Lipidated Atg8a was detected in extracts from wild-type but not *Atg7*-null midguts, suggesting that it is not essential for autophagy in midgut cells. In line with this, autophagy in this setting was also independent of Atg3, the E2-conjugating enzyme for Atg8a lipidation. Further experiments showed that ubiquitin is required for the formation of Atg8a-positive puncta in clones of midgut cells and for their reduction in size. As a decrease in Uba1 activity suppressed the reduction in cell size in response to Atg1, the authors concluded that "Uba1 functions downstream of Atg1-regulated autophagy."

This study presents a new example of ATG-independent autophagy in an *in vivo* setting. It will be interesting to determine the exact role of Uba1 in Atg7- and Atg3-independent autophagy in the *D. melanogaster* midgut.

Katharine H. Wrighton

ORIGINAL RESEARCH PAPER Chang, T. K. *et al.* Uba1 functions in Atg7- and Atg3-independent autophagy. *Nature Cell Biol.* http://dx.doi.org/10.1038/ncb2804 (2013)
FURTHER READING Codogno, P., Mehrpour, M. & Proikas-Cezanne, T. Canonical and non-canonical autophagy: variations on a common theme of self-eating? *Nature Rev. Mol. Cell Biol.* **13**, 7–12 (2012)