

Gluing together the pieces of crinophagy

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Study identifies some of the molecules involved in targeting excess secretory vesicles to lysosomes for degradation.

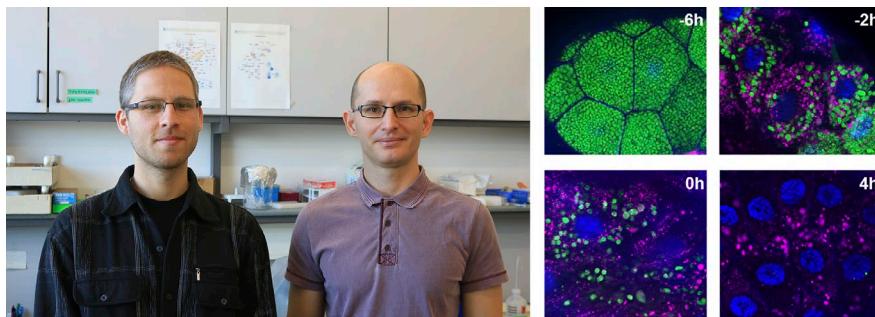
Cytoplasmic material can be targeted to lysosomes for degradation in many different ways. Double membrane-bound autophagosomes can engulf cytoplasmic content and then fuse with lysosomes in a process known as macroautophagy. Alternatively, during microautophagy, small portions of the lysosomal membrane can invaginate and engulf the surrounding cytoplasm, while individual proteins can be specifically delivered to lysosomes via chaperone-mediated autophagy.

A fourth route for lysosomal delivery is crinophagy, in which excess secretory granules fuse directly with lysosomes instead of being delivered to the plasma membrane for exocytosis. Little is known about this process, but, in this issue, Csizmadia et al. identify some of the molecules that control this pathway during a key step in *Drosophila* development (1).

Crinophagy was first described over 50 years ago in the anterior pituitary gland cells of rats (2), and it plays a key role in the degradation of insulin-containing secretory granules in pancreatic β cells (3). “It’s now clear that pretty much every cell that produces secretory granules uses crinophagy to degrade some of them,” explains Gábor Juhász, from Eötvös Loránd University in Budapest and Biological Research Centre in Szeged, Hungary. “But nothing at all is known about the mechanism of crinophagy.”

One reason for crinophagy’s enduring mystery is that there is no good model system for studying the pathway. In cultured cell lines, at least, crinophagy appears to operate continuously at basal levels and researchers have been unable to find ways of stimulating the process.

As fly biologists, however, Juhász and colleagues, including first author Tamás Csizmadia, suspected that crinophagy might be activated in *Drosophila* salivary glands at a critical stage of postembryonic development. Shortly before *Drosophila* larvae form puparia and begin their metamorphosis into adult flies, their salivary glands start to produce large numbers of specialized secretory granules packed with adhesive proteins that, once secreted, can attach the puparium



Focal Point. Tamás Csizmadia (left), Gábor Juhász (right), and colleagues reveal some of the molecular machinery that mediates crinophagy, a process in which excess secretory granules directly fuse with lysosomes so that their contents can be degraded instead of being exocytosed at the plasma membrane. 6 h before *Drosophila* larvae form a puparium and undergo metamorphosis, their salivary gland cells are packed with glue granules (green) containing secretory proteins that can attach the puparium to solid surfaces. At the onset of metamorphosis (0 h), glue granules colocalize with lysosomes (magenta) and are degraded. Csizmadia et al. reveal that glue granule–lysosome fusion requires several factors, including specific SNARE proteins, Rab GTPases, and the HOPS tethering complex. PHOTO COURTESY OF THE AUTHORS.

to a solid surface (4). To ensure successful attachment, these so-called glue granules are produced in excess but, after the onset of metamorphosis, the remaining granules might be degraded by crinophagy.

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Csizmadia et al. confirmed that crinophagy is activated in salivary gland cells at the onset of metamorphosis, using several fluorescent reporter proteins to monitor the delivery of glue granule proteins to acidic, degradative lysosomes (1). The delivery of glue granules to lysosomes did not require the regular autophagy machinery that assembles autophagosomes. However, when Csizmadia et al. used RNAi to deplete trafficking proteins that target autophagosomes to lysosomes, they found that many of these factors were also required for glue granule–lysosome fusion, including the HOPS tethering complex, the GTPases Rab2 and Rab7, and the SNARE proteins Snap29 and Vamp7.

“But there was one difference in the SNARE proteins involved,” Juhász says. “The key SNARE for autophagosome–lysosome fusion is Syntaxin 17 but we

found that this protein isn’t required for glue granule–lysosome fusion.”

Juhász and colleagues therefore tested SNARE proteins similar to Syntaxin 17 and determined that Syntaxin 13 plays the equivalent role in crinophagy, interacting with Snap29 and Vamp7 to mediate glue granule–lysosome fusion. Based on their initial localization data, Csizmadia et al. suggest a model in which Syntaxin 13 is present on glue granules along with Rab7, which, by recruiting the HOPS complex, helps tether Rab2-positive lysosomes, leading to SNARE complex assembly and membrane fusion.

These same factors are highly likely to be required for crinophagy in mammalian cells as well. “The next question for us is: What is the developmental trigger for crinophagy in *Drosophila* salivary gland cells?” Juhász says. “We’re currently screening known signaling proteins to see whether there is a dedicated pathway that stimulates glue granule–lysosome fusion at the onset of metamorphosis.”

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4. Beckendorf, S.K., and F.C. Kafatos. 1976. *Cell.* 9:365–373.

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