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AUTOPHAGY

Who presses the self-destruct button?

Because peroxisomes carry out many important metabolic functions, their selective degradation through autophagy, known as pexophagy, is important for homeostasis and for regulation of metabolism. Here, Hettema and colleagues attempt to delineate the mechanisms of pexophagy in *Saccharomyces cerevisiae* and describe a new protein, Atg36, that has a key role in this process.

Previous studies had shown that the peroxisomal membrane protein Pex3, which has a role in peroxisome formation and segregation, is also involved in pexophagy in methylotrophic yeast (such as *Pichia pastoris*). Using a yeast two-hybrid screen, the authors identified Atg36 as a candidate Pex3-interacting protein in *S. cerevisiae*. Further analysis showed that Atg36 bound directly to Pex3 *in vitro* and *in vivo*, and that Atg36 colocalized with Pex3 at the peroxisomal membrane. This indicates that Pex3 recruits Atg36 to peroxisomes.

> “Atg36 is specifically required for pexophagy.”

Next, the authors sought to examine the role of Atg36 in peroxisomes. They observed that Atg36-deficient cells had more peroxisomes than with wild-type cells and were resistant to peroxisome breakdown in starvation conditions as well as in the post-log growth phase. Furthermore, cells overexpressing Atg36 showed higher levels of pexophagy under starvation conditions than wild-type cells. Importantly, Atg36-deficient cells did not have defects in non-selective autophagy or in other selective autophagy pathways. Together, these findings suggest that Atg36 is specifically required for pexophagy.

So how does Atg36 activate pexophagy? Selective autophagy is thought to be mediated by the adaptor protein Atg11, which links the receptors for specific cargo to the core autophagic machinery. Consistent with this, Atg36 co-immunoprecipitated with Atg11 in lysates from cells grown under starvation conditions. Moreover, using cells in which autophagy is blocked but which still form pre-autophagosomal structures, the authors found that Atg11 colocalized with peroxisomes when Atg36 was present but not when it was absent. Thus, the authors conclude that Atg36 is the selective receptor required for pexophagy.

Furthermore, the authors show that Atg36 acts as a selective autophagy receptor: Atg36 localized at mitochondria when Pex3 was redirected there and functionally replaced the receptor for selective mitophagy.

Finally, the authors examined whether the role of Pex3 in pexophagy is independent of its functions in peroxisome biogenesis and segregation. By screening a library of *pex3* mutants, they identified three mutants that had a similar phenotype to Atg36-deficient cells, and observed that the pexophagy defect was due to an inability to bind Atg36. Because one of these mutants, *pex3-177*, showed defects only in pexophagy and not in peroxisome biogenesis and segregation, they conclude that the role of Pex3 in pexophagy is genetically distinct from its other functions.

Together, these findings suggest that Pex3 localizes Atg36 to peroxisomes, where it binds the adaptor protein Atg11 to mediate pexophagy. Interestingly, the authors observed that Atg36 was modified to become activated, so further work is needed to determine which post-translational modifications are required and how these result in binding to Atg11.

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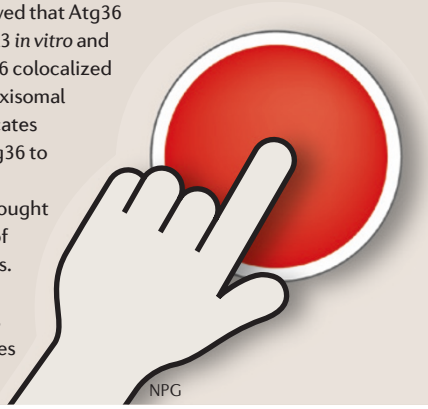

ORIGINAL RESEARCH PAPER Motley, A. M., Nuttall, J. M. & Hettema, E. H. Pex3-anchored Atg36 tags peroxisomes for degradation in *Saccaromyces cerevisiae*. *EMBO J.* 29 May 2012 (doi:10.1038/emboj.2012.151)