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AUTOPHAGY

Selecting ER for eating

> Both studies identify receptors that associate with the ER and target it for ER-phagy

Two studies in *Nature* provide important mechanistic insight into the autophagy-mediated degradation of the endoplasmic reticulum (ER), which is known as 'ER-phagy'. Both studies identify receptors that associate with the ER and target it for ER-phagy; Mochida *et al.* show that autophagy-related (Atg) proteins Atg39 and Atg40 perform this role in yeast, and Khaminets *et al.* reveal that FAM134B (the mammalian counterpart of Atg40) does so in mammalian cells and in mice.

Atg8 (LC3 in mammals), which is present on autophagosomal membranes, binds to autophagy receptors that target specific cellular organelles for autophagy. Mochida *et al.* identified the uncharacterized proteins Ylr312c and Yor152c, which they named Atg39 and Atg40, respectively, as Atg8-interacting proteins in *Saccharomyces cerevisiae*. Atg39 and Atg40 have an Atg8-interacting motif that is commonly found in autophagy receptors, and mutations in this motif abolished their interaction with Atg8, suggesting that Atg39 and Atg40 are autophagy receptors. When imaging ER membrane dynamics using a GFP-tagged version of the ER membrane protein Sec63, Mochida *et al.* observed that knockout of *ATG39* and *ATG40* almost abolished ER-phagy, whereas overexpressing these proteins promoted it. Thus, Atg39 and Atg40 are receptors for ER-phagy.

GOODSHOOT

Yeast contain perinuclear ER (pnER), which is equivalent to the nuclear envelope, and cortical ER (cER); both are connected to cytoplasmic ER (cytoER). Mochida *et al.* found that deletion mutants of Atg40, which is predominantly found in the cER and cytoER, reduced the degradation of folded tubes and sheets of these ER subdomains. By contrast, Atg39 localized to pnER, and Atg39 depletion mutants decreased the degradation of double-ring structures of pnER that contain inner and outer nuclear membrane proteins. Thus, the authors propose that Atg39 and Atg40 have specific roles in ER-phagy and that Atg39-mediated autophagy should also be referred to as nucleophagy.

Khaminets *et al.* searched for novel autophagy receptors that bind to LC3 and GABARAP (another mammalian orthologue of Atg8) and found that FAM134A, FAM134B and FAM134C, which contain a reticulon homology domain (this domain is also found in Atg40), interact with both proteins in mammalian cells. Mutations in the putative LC3-interacting region (LIR) motif in FAM134B abolished FAM134B–LC3 interactions, and FAM134B mutants lacking the LIR motif could not bind to LC3. Thus, FAM134 proteins are likely to be autophagy receptors. Further experiments showed that FAM134B colocalizes with markers of sheet-like cisternal ER (marked by CLIMP63) and tubular ER (marked by RTN4) and that overexpression of FAM134B in mammalian cells causes ER fragmentation, an increase in autophagosome-associated ER structures and the degradation of ER-associated proteins. By contrast, knockdown of *FAM134B* led to ER expansion, confirming that FAM134B is an ER-phagy receptor in mammalian cells.

To analyse the role of FAM134 proteins *in vivo*, Khaminets *et al.* disrupted the gene encoding FAM134B in mice. They found that the ER was expanded in isolated mouse embryonic fibroblasts and in the sensory neurons of 10-month-old mice. Moreover, they observed that ER expansion was correlated with a decrease in the number of sensory neurons, probably because disrupted ER homeostasis sensitized these cells to cell death. This is of clinical importance, as mutations in *FAM134B* cause sensory neuropathy in humans.

In summary, these studies suggest that the mechanism of ER-phagy is at least partially conserved from yeast to mammals and that FAM134B is likely to be the mammalian counterpart of Atg40.

Katharine H. Wrighton

ORIGINAL RESEARCH PAPERS Mochida, K. *et al.* Receptor-mediated selective autophagy degrades the endoplasmic reticulum and the nucleus. *Nature* http://dx.doi.org/10.1038/nature14506 (2015) | Khaminets, A. *et al.* Regulation of endoplasmic reticulum turnover by selective autophagy. *Nature* http://dx.doi.org/10.1038/nature14498 (2015)