Receptors for selective recycling

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Two studies show that the engulfment of certain intracellular membranous structures by vesicles called autophagosomes, is a selective, receptor-protein mediated process, which regulates their degradation

Macroautophagy (henceforth autophagy) is a conserved pathway that enables the lysosomal degradation of intracytoplasmic contents which are first engulfed by double-membraned autophagosomes. This process was initially considered to be primarily a bulk process for degradation of intracytoplasmic contents, including organelles like mitochondria and the endoplasmic reticulum (ER), aggregate-prone proteins and various infectious agents. Recent studies have suggested that such cargoes can be selectively incorporated into autophagosomes[1]. This issue of Nature includes two complementary studies in mammalian and yeast systems that identify specific receptor proteins that enable the selective autophagic degradation of the ER [2,3].

The first recognisable precursors for autophagosomes are cup-shaped double membrane structures called phagophores. Prior experiments had suggested that selective autophagy of certain bacteria, mitochondria and aggregate-prone proteins was mediated via so-called autophagy receptors which bind phagophore and autophagosome machinery components like the Atg8 family member LC3 via interactions with the LC3-interacting domains (LIRs in mammalian cells or Atg8-binding pockets in yeast). Distinct domains of these receptors bind their cargoes[1].

The phenomenon of ER degradation by autophagy (ER-phagy) has been described previously and this may be clinically important for diseases like α_1-antitrypsin deficiency, where the

accumulation of the toxic ER-trafficked mutant α_1-antitrypsin causes liver damage[4]. The clearance of this protein from the ER is at least partly dependent on autophagy and autophagy-enhancing compounds can attenuate the toxicity of the protein in vivo [4]. A key issue that has been raised by the current studies is whether the ER-phagy is merely part of bulk autophagy, or whether there is machinery that enables preferential selection of ER into autophagosomes. Interestingly, Tamotsu Yoshimori's lab hypothesised the possibility of selective ER-phagy in their 2006 study: "Although it has been widely accepted that autophagic sequestration is a non-specific bulk process, our data suggest that α_1-antitrypsin is delivered to autophagosomes in a more efficient manner than a control cytosolic protein EYFP" [5].

These two current studies provide robust support for this prediction and describe mechanisms. The key starting point for both studies was the identification of autophagy receptors by searching for LC3/Atg8 interactors. The mammalian interactor FAM134B is a protein with a functional LIR domain and a reticulon domain (a domain frequently associated with the ER)[3] and the yeast proteins[2] are Atg40, which appears to be a counterpart of FAM134B and Atg39. These proteins bind Atg8/LC3 on the one hand and interact with the ER on the other. Loss of these proteins does not affect bulk autophagy in mammalian systems or in yeast, but does affect the degradation of the ER in an autophagy-dependent manner. Mutants of these proteins that do not bind the autophagy machinery are ineffective at ER-phagy[2,3].

The studies raise fascinating questions relevant to physiology and disease processes. The yeast work reports that Atg39 is associated with the perinuclear ER (the nuclear envelope) and that it regulates the degradation of both nuclear envelope as well as some nuclear constituents[2]. This introduces an additional concept of selective autophagy of the nucleus, which they term nucleophagy. It will be interesting to understand when the nuclear envelope is degraded, which components are degraded, and why this process is required for this compartment. Atg40, on the other hand is associated with cortical and cytoplasmic ER and appears to target the degradation of these compartments.

FAM134B raises additional insights. The data suggests that this protein may play a role in ER-remodelling. It is possible that this protein helps to fragment the ER into bite-sized pieces that can be readily incorporated into autophagosomes[3], in a manner analogous to the model that mitochondrial fission enables the autophagic sequestration and degradation of mitochondria[6].

FAM134B is also interesting as it is mutated in an autosomal recessive human sensory neuropathy where the patients have impaired pain perception resulting in mutilating ulceration of the hands and feet[7]. The authors have studied a FAM134B knockout mouse model in which they characterise sensory defects compatible with the human condition[3]. These mice also accumulate ER in the cell bodies of the sensory neurons before obvious

morphological abnormalities are apparent. This raises the interesting idea that ER-phagy may be critical particularly in these pain neurons, although at the moment it is difficult to know if the sensory abnormalities are mediated by autophagy-independent roles of FAM134B. (The suggestions that ER-phagy may be important for cellular health is supported by the increased sensitivity of Atg39-deficient yeast to nitrogen starvation[2].) If the sensory abnormality is directly due to the increased ER volume, it will be important to know if this is simply due to toxic effects of the uncleared material, or if the increased ER volume and area impacts on signalling and neurotransmission. If the latter contributes, then this may be pathway with therapeutic possibilities.

In summary, these two complementary studies have identified possibly functional orthologous systems which regulate ER degradation via autophagy. The discovery of these autophagy receptors will enable further elucidation of the process, its importance and its regulation. Key questions that emerge include understanding the relevance of this machinery to nuclear homeostasis in mammalian cells, exploration of the consequences of impaired or excessive ER-phagy, and elucidation of how the process is regulated. The activities of many autophagy receptors can be modulated by post-translational modifications like phosphorylation[1]. It will be interesting to understand if such mechanisms are pertinent to ER-phagy. Indeed, the yeast study may provide clues as it reports increased levels of Atg39 and Atg40 when cells were treated with rapamycin, which induces some signalling changes seen with nitrogen starvation. Finally, is there a selectivity as to which parts of the ER/nuclear envelope are cleared by this pathway? If so, what is selected and why?

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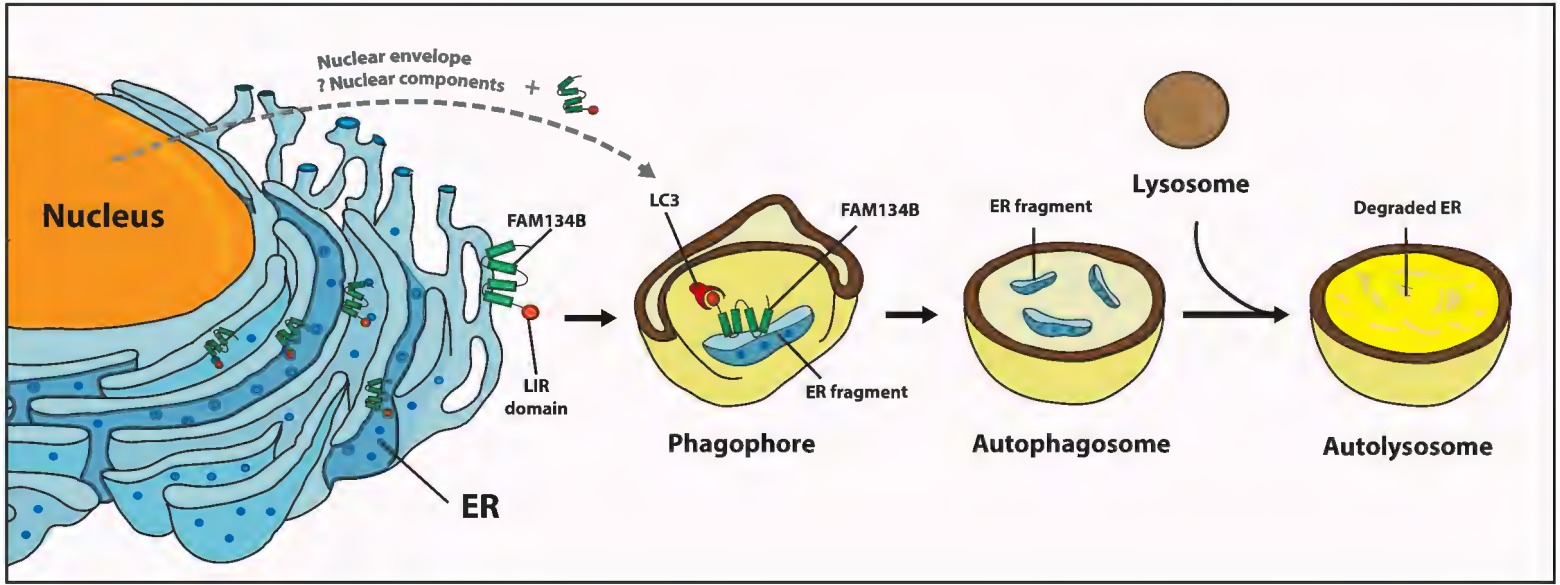
Figure legend:

Schematic overview of ER-phagy. The mammalian receptor is shown for simplicity (but the yeast receptors are Atg39 and Atg40). Some key questions emerging from these studies are highlighted.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