Up for grabs; trashing peroxisomes

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Together with the proteasome, autophagy is one of the major catabolic pathways of the cell. In response to cellular needs or environmental cues, this transport route targets specific structures for degradation into the mammalian lysosomes or the yeast and plant vacuoles. The mechanisms allowing exclusive autophagic elimination of unwanted structures are currently the object of intensive investigations. The emerging picture is that there is a series of autophagy receptors that determines the specificity of the different selective types of autophagy. How cargo binding and recognition is regulated by these receptors, however, is largely unknown. In their study, Motley *et al* (2012) have shed light into the molecular principles underlying the turnover of excess peroxisomes in the budding yeast *Saccharomyces cerevisiae*.

Peroxisomes perform a series of crucial functions and their number is regulated in response to the metabolic demands of the cell. After proliferation and when no more required, a selective type of autophagy called pexophagy degrades superfluous peroxisomes (Manjithaya *et al*, 2010). This turnover allows the cell to save the energy required for the maintenance of excess organelles and to generate metabolites that can be used to carry out other functions. Like all selective types of autophagy, pexophagy relies on the conserved core of the autophagy-related (Atg) machinery, but also requires additional proteins that confer specificity of the pathway such as cargo selection and membrane dynamics (Manjithaya *et al*, 2010). It is still unclear, however, which

peroxisomal protein allows the recognition of peroxisomes by the autophagosomes. Although Pex3 and Pex14 have previously been indicated as possible suspects (Bellu *et al*, 2001, 2002; Farre *et al*, 2008), their specific contribution to pexophagy was difficult to establish. Deletion of either *PEX3* or *PEX14*, as well as most other *PEX* genes, leads to defects in

Figure 1 Schematic representation for a putative Pex3 checkpoint. The peroxisomal integral membrane protein Pex3 acts as a master regulator to determine peroxisome fate. Organelle abundance is regulated by formation of new organelles, and their subsequent segregation (inheritance) and degradation. A new paradigm has been uncovered, whereby Pex3 controls peroxisome abundance through the regulated binding to specific co-factors. At the endoplasmic reticulum (ER), together with Pex19, it initiates biogenesis of new peroxisomes. At the peroxisomal membrane, it ensures that both mother and daughter cells obtain the correct number of peroxisomes, whereas when the organelles become dispensable, Pex3 can initiate their selective degradation. To keep peroxisomes in the mother cell during cell division, Pex3 associates with Inp1 and tether peroxisomes to cortical actin patches. Under pexophagy-inducing conditions, Pex3 binds the newly identified pexophagy factor Atg36 and delivers peroxisomes to the site of autophagosome formation for subsequent degradation into the vacuole.

peroxisome biogenesis, which makes the dissection of their contribution to peroxisome degradation very difficult to assess. Motley *et al* (2012) have elegantly exploited *S. cerevisiae* genetics to isolate *pex3* alleles specifically impaired in pexophagy and could thus demonstrate that Pex3 (and not Pex14) mediates the selective engulfment of peroxisomes by autophagosomes. In support to this result, the authors have also identified a new protein, Atg36, which binds Pex3 (Figure 1). Importantly, Atg36 interacts with Atg11, an autophagy adaptor involved in numerous selective types of autophagy in yeast, thereby bringing peroxisomes to the site where autophagosomes will be generated and coordinating the activation of the Atg machinery at this location (Kim *et al*, 2001; Reggiori *et al*, 2005; Monastyrska *et al*, 2008). Atg36, however, is only present in *S. cerevisiae* and related yeasts. Methylophilic yeasts, in contrast, appear to have a different protein with the same properties, Atg30 (Farre *et al*, 2008). It is unclear, however, whether Atg30 is the functional counterpart of Atg36 because these two proteins do not display similarities in their amino-acid sequence.

While it is unmistakable that Atg36 (and Atg30) is essential for pexophagy, it remains unclear whether this protein is an autophagy receptor. This class of molecules has four characteristics (Kraft *et al*, 2010). First, each autophagy receptor binds a specific cargo. Second, they often interact with adaptor proteins, which function as scaffolds that bring the cargo-receptor complex in contact with the core Atg machinery to allow the specific sequestration of the cargo. Third, they possess at least one LC3-interacting region (LIR) motif that enables them to interact with the LC3/Atg8 pool present in the interior autophagosomes and assures the hermetic enwrapping of the cargo into these vesicles. Fourth, autophagy receptors are degraded in the lysosome/vacuole together with the cargo that they bind to. While Atg36 (and Atg30) binds both the cargo and the adaptor protein Atg11,

this protein does not appear to be turned over in the vacuole during pexophagy and a LIR motif has not been pinpointed yet. Consequently, it is unclear whether Atg36 is a new type of autophagy receptor or acts together with a not yet identified autophagy receptor involved in pexophagy.

A very interesting concept emerging from the work of Motley *et al* (2012) is that a single protein, that is, Pex3, could be the central regulator of peroxisome homeostasis (Figure 1). Pex3 is involved in peroxisome biogenesis, segregation and degradation (Bellu *et al*, 2002; Hoepfner *et al*, 2005; Farre *et al*, 2008; Munck *et al*, 2009; Ma *et al*, 2011). As a result, the cell could regulate peroxisome abundance by modulating Pex3 function and/or its array of interactions. In this context, it would be particularly interesting to determine whether Pex3 is also the decision maker of a quality control mechanism that eliminates peroxisomes when not correctly assembled and thus dysfunctional, or when not accurately distributed during cell division. Clearly, additional experiments are needed to understand how Pex3 regulates peroxisome homeostasis, but this protein and this organelle could represent a convenient system to unveil the principles that regulate the steady-state level of other subcellular compartments.

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Conflict of interest

The authors declare that they have no conflict of interest.

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