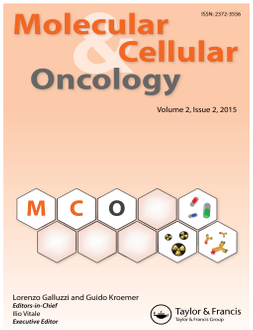

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AUTHOR'S VIEW

# Specific COPII vesicles transport ER membranes to sites of autophagosome formation

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**ABSTRACT**
The endoplasmic reticulum (ER) is considered a prominent membrane source for the formation of autophagosomes. Recent results from our laboratory revealed a cellular mechanism for the contribution of the ER to autophagosomes in yeast: membranes, together with unconventional membrane fusion machinery, are delivered to sites of autophagosome formation by specific coat protein complex II (COPII) vesicles.

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## Main text

Autophagy is a conserved cellular process characterized by the *de novo* generation of double-membraned autophagosomes with a central function in promoting survival during periods of starvation. Autophagosomes enclose bulk cytosol during their formation and, after closure, are transported to the vacuole/lysosome where their content is degraded and recycled. Additional and more specialized functions of autophagy include cellular quality control such as the removal of aggregated proteins or damaged organelles. Recent studies also implicate autophagy in the regulation of non-apoptotic cell death during development.[1] Given that autophagy is broadly involved in many key aspects of cellular homeostasis, it is not surprising that its dysfunction contributes to various human diseases, among them neurodegenerative diseases and cancer.[2]

Crucial insight to understanding the cellular mechanisms of autophagosome formation comes from studying the origin of their membranes as well as the processes that fuse and shape these membranes.[3] One key message that has emerged from numerous studies in recent years is that multiple cellular sources can provide membranes to autophagosomes, apparently in a context- and cell-specific manner.[4] Another key discovery was the involvement of soluble N-ethyl-maleimide-sensitive factor attachment protein receptors (SNAREs) in autophagosome formation, both in yeast and in mammals.[5, 6] Thus, membrane fusions that lead to the integration of distinct membrane pools for the biogenesis of autophagosomes are at least in part catalyzed by the same basic cellular mechanisms that also regulate fusions of transport vesicles with organelles along the secretory and endocytic pathways.[7]

With this in mind, and considering the well-established fact that the endoplasmic reticulum (ER) is a conserved and major source of membranes for autophagosomes, we investigated whether and how ER-localized membrane fusion machineries contribute to the formation of autophagosomes in yeast. We found that the SNARE protein Ufe1, which was previously known for its role in both homotypic ER-ER membrane fusion and heterotypic fusion of retrograde vesicles with the ER membrane, is also required for autophagy.[8] Interestingly, the largely ER-resident Ufe1 was increasingly exported from the ER and routed to the vacuole under conditions that triggered autophagy, i.e., under cellular starvation. Furthermore, Ufe1 transiently co-localized and physically interacted with the autophagy marker proteins Atg8 and Atg9, the latter being an integral membrane protein and prominent component of a pool of cytosolic vesicles that are considered another major source of membranes for autophagosomes. Moreover, ultimate vacuolar uptake of Ufe1 did not depend on autophagosomes, but on multivesicular bodies (MVBs). These findings together supported the idea that Ufe1 was not exported from the ER as a substrate of autophagy but because it might function in membrane fusion events outside the ER that are linked to autophagosome biogenesis. Support for such a scenario came from our findings that Ufe1 physically interacted with other non-ER SNAREs that had previously been implicated in the formation of autophagosomes.[8]

In a subsequent series of experiments we analyzed in more detail the role of Ufe1 in membrane supply to autophagosomes. The key methods used involved thin-section electron microscopy and confocal fluorescence microscopy in combination with 3-dimensional reconstruction. Under conditions where Ufe1 was inactive both autophagosome size and number were significantly reduced compared to control cells. These results indicated a decrease in membrane supply to autophagosomes analogous to results obtained from studying the role of Atg9 in autophagy.[9]

Independent evidence for a role of Ufe1 and Ufe1-containing ER membranes in autophagosome formation, which also eliminated the potential caveat of indirect effects obtained from experiments with conditionally inactive Ufe1, came from experiments where we addressed the pathway by

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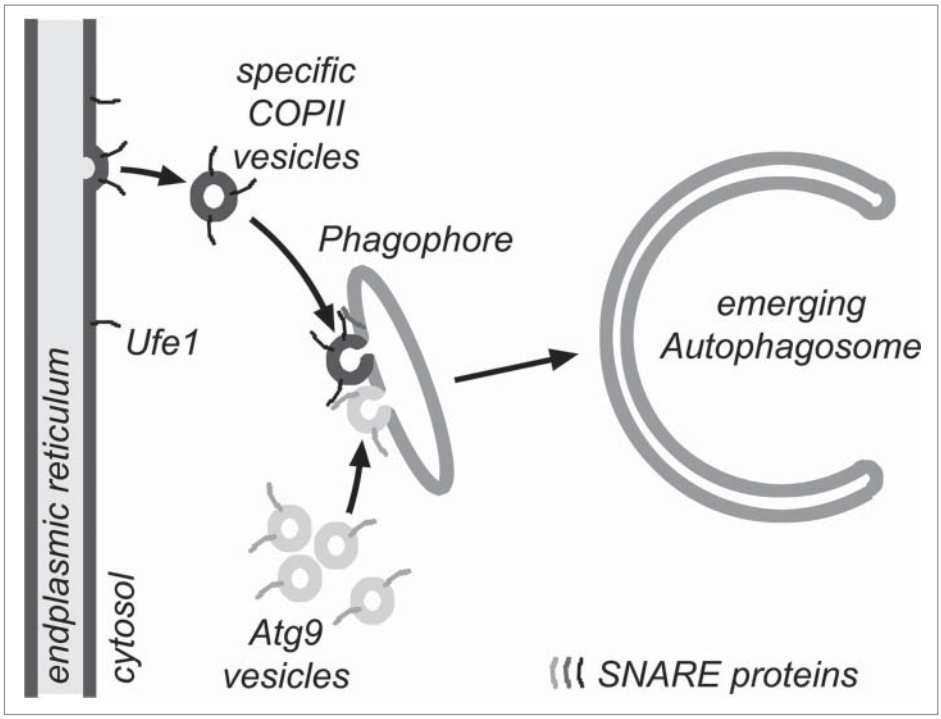


**Figure 1.** Model for the contribution of endoplasmic reticulum (ER) membranes to autophagosome biogenesis via vesicular transport. Ufe1, an ER-resident Qa/t-SNARE protein, is incorporated into specific coat protein complex II (COPII) vesicles that form upon conditions that trigger autophagy. The COPII vesicles are targeted to sites of autophagosome formation where they fuse with other membrane sources, such as Atg9-containing vesicles, to form a phagophore that through continuous expansion will give rise to an autophagosome. Ufe1 itself might participate in such membrane fusions by forming complexes with distinct SNARE proteins that are present on other membranes. The identity of the individual partner SNARE proteins for the particular fusion reactions remains to be determined. A specific membrane fusion requires the participation of 3 to 4 distinct SNARE proteins but for simplicity fewer individual SNARE proteins are shown here.

which Ufe1 was exported from the ER upon starvation. ER exit of Ufe1 relied on the early secretory pathway, and in particular on coat protein complex II (COPII) vesicles. Interestingly, the particular COPII mutant that contained the temperature-sensitive *sec23–1* allele showed a strong reduction in Ufe1 ER export even at the permissive temperature. Under the same conditions, transport of conventional cargo was unaffected. This observation provided us with a tool to measure the correlation between reduced ER exit of Ufe1 and the biogenesis of autophagosomes. Remarkably, *sec23–1* cells were hypersensitive to starvation conditions and showed a reduction in autophagic flux at the permissive temperature. At the ultrastructural level we found that *sec23–1* cells produced significantly fewer autophagosomes than control cells. The finding that reduced efficiency of autophagosome biogenesis correlated with reduced ER exit of Ufe1 in *sec23–1* cells suggested that the vesicles that are formed during starvation are specific COPII vesicles that differ from conventional cargo transporters. Our data furthermore suggest that the presence of Ufe1 in such ER vesicles might contribute to their fusion with different membrane pools during the generation of autophagosomes (Fig. 1).

Sec23 is a component of the inner layer of the COPII coat and the phenotypes associated with the *sec23–1* allele could illustrate particular conformations of coat proteins on vesicles with a function in autophagosome formation. Previous work revealed that during starvation of mammalian cells COPII vesicles that are distinct from transport vesicles are formed at the ER-Golgi intermediate compartment (ERGIC) for autophagosome biogenesis.[10] It is thus likely that starvation-dependent formation of specific vesicles from the early secretory pathway, and in particular from the ER, constitutes a universal mechanism to provide membranes for transport to sites of autophagosome formation.

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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