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COMMENTARY

Endomembrane remodeling in autophagic membrane formation

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ABSTRACT

Autophagosomal membrane sources generate autophagic membrane precursors, which later assemble into the double-membrane autophagosome. The key events happening on the membrane sources during autophagic membrane generation remain poorly characterized. Our previous work found the ER-Golgi intermediate compartment (ERGIC) as a membrane source for the phagophore, the precursor to the autophagosome. A relocation of the COPII machinery from the ER-exit sites (ERES) to the ERGIC generates vesicles for LC3 lipidation. In recent work, we made a further step by showing that a starvation-induced remodeling of ERES facilitates the relocation of COPII to the ERGIC and the generation of the autophagic membrane.

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Macroautophagy (thereafter autophagy) is a fundamental cellular process for bulk degradation of cytoplasmic components, which impinges on many human diseases such as cancer, neurodegeneration, and metabolic syndromes. Autophagy is controlled by cascades of signaling pathways that converge on the action of autophagy-related (ATG) proteins. The ATG proteins orderly assemble into several major complexes at the phagophore assembly site (PAS), which nucleates the formation of a double-membrane autophagosome. The phagophore encapsulates cytoplasmic components and after maturation into an autophagosome delivers them to the lysosome for degradation.

Autophagy progresses through multiple membrane remodeling events. At least 4 major events happen. 1) A yet-to-be-defined membrane conversion from the intracellular membrane to the autophagic membrane precursors; 2) autophagic membrane assembly on the PAS, including formation of the cup-shaped phagophore and later completion of the autophagosome; 3) autophagosome fusion with the endosome or lysosome; 4) autolysosome tubulation to regenerate nascent lysosomes (lysosome reformation) (Figure 1A). These events are essential to regulate autophagosome biogenesis and the autophagy-mediated degradation of cytoplasmic components.

In this punctum, we focus on the molecular aspects of step 1, the initial stage of autophagic membrane generation. Evidence indicates that the autophagic membranes are originated from the existing membrane compartments, for example, the endoplasmic reticulum (ER)-Golgi trafficking system, and the plasma membrane. However, it remains unclear how these donor compartments convert their membranes to the autophagosomal precursors. Previously, we developed a cell-free assay to reconstitute an early step of autophagic membrane formation based on analyzing LC3 lipidation, a marker of the autophagic membrane. We found that the ER-Golgi intermediate compartment (ERGIC) provides membrane sources for LC3 lipidation. We subsequently found that a relocation of COPII from its usual reservoir, the ER-exit sites (ERES), to the ERGIC generates ERGIC-COPII vesicles as membrane templates triggering LC3 lipidation. A key question is how COPII relocates from the ERES to the ERGIC. In a recent work, we employed super-resolution imaging, stochastic optical reconstruction microscopy (STORM), to analyze the morphology of the ERES and the ERGIC. Interestingly, we found that starvation induced a remodeling of the ERES positive for the COPII assembly activator PREB/SEC12 (Figure 1B-D). We then identified 2 proteins, CTAGE5 and RB1CC1/FIP200, which are required for the remodeling of the PREB/SEC12-ERES (Figure 1B-D). Depletion of either one of them affects the relocation of COPII from the ERES to the ERGIC as well as autophagosome biogenesis.

Our data suggest a model wherein the remodeling of the ERES-ERGIC-COPII membrane system serves as a pathway to generate the autophagic membrane precursors. Under steady state, COPII vesicles (ER-COPII) are generated from the ERES for ER-Golgi membrane trafficking (Figure 1B). Upon starvation, the PREB/SEC12-ERES is enlarged possibly leading to the concentration of PREB/SEC12 and increased association with the ERGIC (Figure 1C). The ERES-localized PREB/SEC12 then relocates to the ERGIC to trigger COPII vesicle formation (Figure 1D). Our previous results indicated that these ERGIC-COPII vesicles act as membrane templates for LC3 lipidation (Figure 1D). It is likely that these lipidated vesicles are membrane precursors for the phagophore, although this conclusion is pending more direct evidence.

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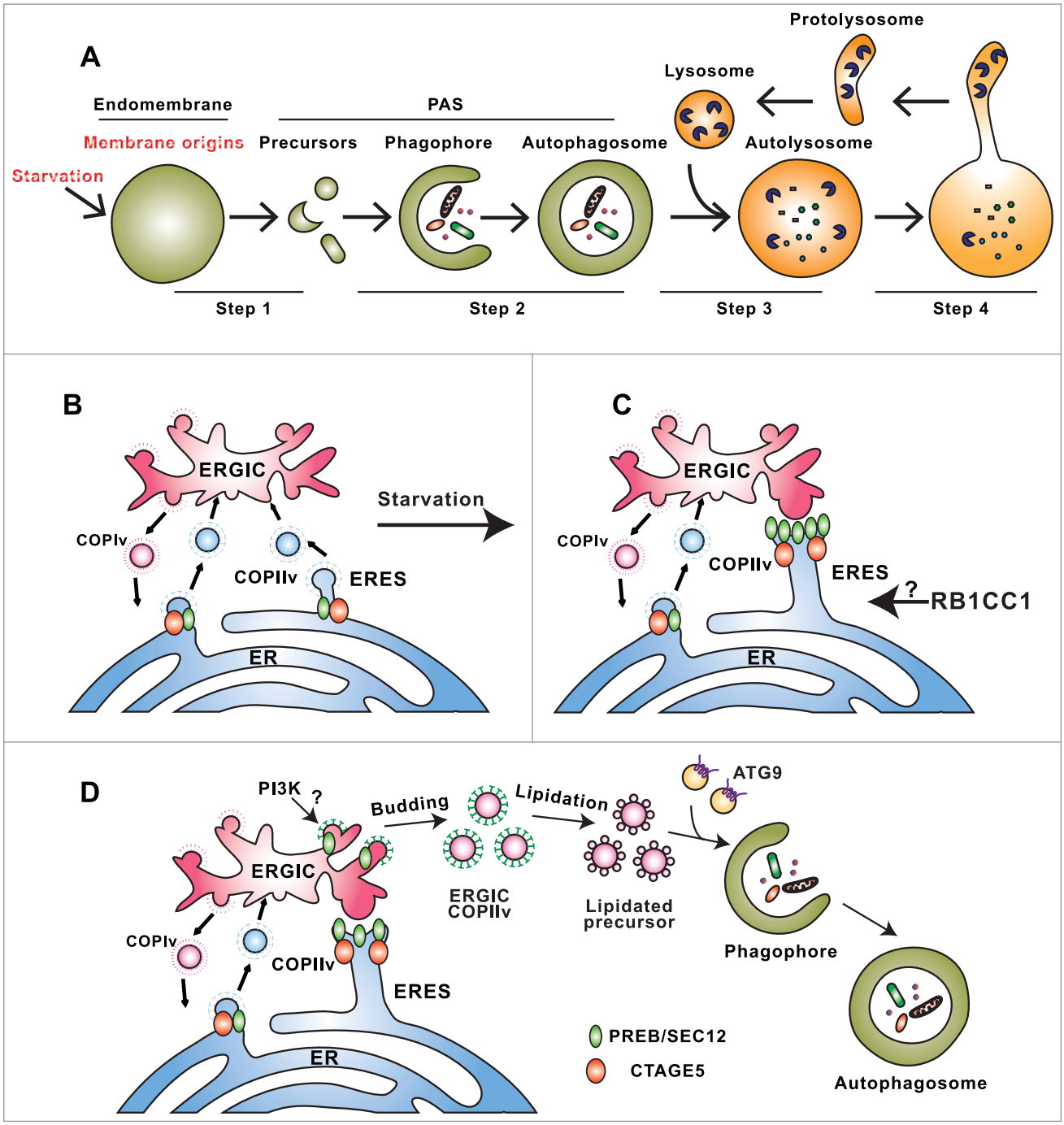

Figure 1. Membrane remodeling during autophagy. (A) An overview of different steps of membrane remodeling in autophagy. (B-D) Remodeling of the ERES-ERGIC-COPII membrane system in autophagic membrane generation. COPIv, COPI vesicle; COPIIv, COPII vesicle.

One interesting observation is that a special pool of RB1CC1, likely enriched in the ERES-ERGIC region, acts in PREB/SEC12-ERES remodeling independent of ULK1 and ATG13. How does RB1CC1 facilitate the remodeling of PREB/SEC12-ERES? One hypothesis is that RB1CC1 may associate with PREB/SEC12 and tether adjacent PREB/SEC12-ERES to induce membrane enlargement. This is based on the structural study of the yeast RB1CC1 homolog Atg17, which has been implicated in forming a scaffold and cooperates with Atg1 to tether highly curved vesicles. It is important in the future to establish a membrane tethering assay as well as resolving the RB1CC1 protein structure in complex with PREB/SEC12 or other key proteins to test this hypothesis.

The downstream effect of PREB/SEC12-ERES remodeling is the relocation of PREB/SEC12 to the ERGIC, which triggers the formation of ERGIC-COPII vesicles. Our study together with others indicates that COPII vesicles may directly enter into the process of autophagic membrane assembly. Several questions remain to be answered: 1) How are these COPII vesicles delivered to the PAS? 2) Could these COPII vesicles directly fuse with membranes from other sources, e.g. the ATG9 vesicle? 3) What is the composition of these COPII

vesicles and do they contribute to the unique content of the autophagic membrane?

Our work indicates that a coordination of ERES-ERGIC-COPII remodeling acts in the process of membrane conversion from the endomembrane source to the autophagic membrane. In addition to our observation, several other groups also reported the remodeling of the intracellular membranes that supports autophagosome biogenesis. For example, the Ktistakis, Yoshimori, and Yamamoto groups reported an ER membrane reshuffling event generating the omegasome as a harbor for autophagic membrane assembly; and the Tooze lab found a change of Golgi structure that likely produces autophagic ATG9 vesicles. These studies consistently indicate the involvement of endomembrane remodeling for the generation of different autophagic membrane precursors.

How a cell builds up the autophagosomal membrane has not yet been fully understood. Our data support the notion of a direct membrane contribution from the endomembrane system to the autophagic membrane. However, we do not rule out the possibility of local membrane synthesis or transfer that may contribute to the assembly of the autophagic membrane. A recent study performed by the Mizushima group indicates that CDIPT/phosphatidylinositol synthase associates with the phagophore, likely supplying phosphatidylinositols for the autophagic membrane. Therefore it is possible that a combination of direct membrane contribution and local phospholipid synthesis and/or transfer produces the autophagic membrane.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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