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Lipid droplets regulate autophagosome biogenesis

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The source of the autophagic membrane and the regulation of autophagosome biogenesis are still elusive open issues in the field of autophagy. In our recent study of the role of lipid droplets (LDs) and their constituents in autophagy, we provided evidence that both the biogenesis of LDs and its lipolysis by specific lipases are important for autophagosome biogenesis. Our study sheds new light on the source of the autophagic membrane and suggests that a flow of membranes from the endoplasmic reticulum (ER) to LDs, and from LDs to the ER, is essential for autophagosome biogenesis.

Keywords: Atg8, autophagosome biogenesis, autophagy, Ayr1, FAS, fatty acids, Ice2, Ldb16, Ldh1, lipid droplets, steryl ester, triacylglycerols, Yeh1

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Macroautophagy (hereafter termed autophagy) is a major catabolic process responsible for the degradation of cytosolic constituents including organelles in the vacuole/lysosome. Autophagy is initiated by the formation of a cup-shaped vesicle termed the phagophore, which elongates, engulfs parts of the cytoplasm, and seals itself to form the autophagosome, a unique double-membrane structure, which then fuses with the lysosome to degrade its contents. Upon induction of autophagy large amounts of autophagosomes are formed. How the cell orchestrates this membrane demand, and the exact source of the membranes, are still elusive open questions.

Lipid droplets are storage organelles for the neutral lipids present in most cell types. The LD core consists mainly of triacylglycerols (TAGs) and steryl esters (STEs). Evidence points to the ER as the site of formation of the LDs, which we postulated to be the main source of the autophagosomal membrane. A complex relationship between autophagy and LDs was recently described: on the one hand autophagy is implicated in lipophagy, a process of LD degradation, while on the other hand, LDs are linked to autophagy regulation.

In a recent study in yeast we showed that the extent to which autophagy is inhibited by fatty acid synthase (FAS) correlates with the amount of LDs. Based on these results we examined whether LDs are essential to the autophagic process. We found that enzymes responsible for synthesis of the TAGs Dga1 and Lro1 and the STEs Are1 and Are2 are indeed required for the autophagic process. Deletion of these enzymes not only results in inhibition of the autophagic process but also has profound and opposite effects on Atg8 lipidation. Under nitrogen starvation, deletion of the genes encoding the TAG enzymes gives rise to the nonlipidated form of Atg8, whereas deletion of the genes encoding the STEs, or of both the STE and the TAG enzymes, results in the accumulation of Atg8 in its lipidated form. These findings pointed to a possible regulation of the conjugation machinery. Notably, the changes in Atg8 forms of lipidation are observed only upon nitrogen starvation, pointing to a specific effect on autophagy rather than on the cytoplasm-to-vacuole targeting pathway. In agreement, accumulation of unprocessed Ape1 (prApe1) is not observed under growing conditions in any of these mutants. It would be worthwhile to determine the lipid composition of the different LD mutants under nitrogen starvation conditions and also to establish whether Atg8 in these strains is conjugated only to phosphatidylethanolamine.

To further address the role of LDs in autophagy we examined their contribution to the autophagic process. Whereas the well-characterized TAG lipases Tgl3, Tgl4 and Tgl5 have no effect on this process, deletion of the gene encoding the STE lipase Yeh1, the TAG lipase Ayr1, and the lipase/hydrolase Ldh1 lead to inhibition of starvation-induced autophagy. Moreover, Ayr1 and Ldh1 exhibit a synergetic inhibitory effect on the autophagic process, pointing to the importance of LD lipases in autophagy. The observed involvement of LD lipases implies that the contribution of lipids from LDs is needed for autophagosome buildup, and localization of the different lipases under nitrogen starvation may shed light on the origin of the autophagic membrane. Finally, we investigated whether sites of contact between the ER and LDs, thought to funnel lipids between these organelles, play a role in autophagy. We found that both Ice2 and Ldb16, integral membrane proteins essential for the formation of such ER-LD contact sites, are essential players in the autophagic process. Our results thus point to a need for both the ER and LDs in biogenesis of the autophagosome and coincide with the critical role of the ER in autophagosome biogenesis.

In agreement with the close relationship found between the ER and LDs under nitrogen starvation conditions, we observed massive proliferation of the ER in the absence of LDs, suggesting that during nitrogen starvation, membrane flow from the ER to LDs is essential for maintenance of ER morphology. Moreover, our finding that autophagy-deficient strains contribute to the aberrant ER morphology that occurs under nitrogen starvation conditions is consistent with the notion that autophagy plays an important role in the maintenance of ER homeostasis under stress. The knowledge that LDs are required for the autophagic process not only sheds new light on the origin of the autophagosomal membrane, but also tentatively establishes a mechanism by which cells cope with an increasing demand for lipids dedicated to autophagosome biogenesis. Accordingly, cells utilize lipid pools to meet the changes in lipid demand during nitrogen starvation. Notably, we recently demonstrated that FAS is degraded by autophagy and consequently that its activity under nitrogen starvation conditions decreases. Thus, under prolonged starvation periods the cells evidently rely more on lipid stores than on newly synthesized fatty acids. While inhibition of FAS under growing conditions is indeed deleterious, it is much more tolerable during nitrogen starvation, whereas the opposite is true for LDs. Elucidation of the tight regulatory relationships that exist among ER, LDs and autophagy may herald a new approach to the treatment of metabolism-associated diseases.

In a related vein, LDs have recently emerged as organelles that participate in aggregate clearance. On the one hand, the involvement of LDs in autophagosome biogenesis and aggregate clearance, and on the other hand the ability of autophagosomes to deliver LDs to the vacuole/lysosome, may prove to be a key mechanism by which cells eliminate aggregated proteins.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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