Lipid droplet autophagy during energy mobilization, lipid homeostasis and protein quality control

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1. ABSTRACT

Lipid droplets (LDs) have well-established functions as sites for lipid storage and energy mobilization to meet the metabolic demands of cells. However, recent studies have expanded the roles of LDs to protein quality control. Lipophagy, or LD degradation by autophagy, plays a vital role not only in the mobilization of free fatty acids (FFAs) and lipid homeostasis at LDs, but also in the adaptation of cells to certain forms of stress including lipid imbalance. Recent studies have provided new mechanistic insights about the diverse types of lipophagy, in particular microlipophagy. This review summarizes key findings about the mechanisms and functions of lipophagy and highlights a novel function of LD microlipophagy as a mechanism to maintain endoplasmic reticulum (ER) proteostasis under conditions of lipid imbalance.

2. INTRODUCTION

Lipid droplets (LDs) are present from bacteria to metazoans (1-6). In eukaryotes, they are produced at the endoplasmic reticulum (ER) (7, 8). The boundary membrane of LDs is a single phospholipid monolayer, which contains conserved integral and peripheral membrane proteins and envelops a hydrophobic core composed primarily of triacylglycerol (TAG) and sterol esters (SE) (9). LDs are sites of lipid storage and mobilization for energy homeostasis and membrane biogenesis (10). They also store hydrophobic vitamins and lipid signaling molecules, and sequester toxic lipids. Finally, emerging evidence support a role for LDs in protein storage, assembly, and quality control (10, 11).

To use lipids and other compounds stored in LDs, cells have developed mechanisms to transfer LD contents to other compartments. Lipolysis is the best-characterized pathway for release of lipids from LDs. In response to depletion of extracellular free fatty acids (FFA) or the need for mobilization of energy stores, protein kinases including cAMP-dependent protein kinase (PKA) and 5-AMP activated protein kinase (AMPK) are activated by hormonal cues (12). This results in the phosphorylation of cytosolic neutral lipid lipases (adipose triglyceride lipase, ATGL and hormone sensitive lipase, HSL), and of perilipins (PLIN), a conserved family of proteins that serve as scaffolds and regulators on the LD surface (13). ATGL and HSL are then recruited to PLIN proteins on LDs where they catalyze the breakdown of neutral lipids within LDs to generate FFAs that are released from LDs (14).
Other studies indicate that the ubiquitin-proteasome system (UPS) remodels LDs and regulates LD activity. Specifically, when lipid availability is limiting and LD abundance is low, LD proteins including PLIN1 and PLIN2, ATGL and its inhibitor GOS2, and the LD fusion protein FSP27/CIDEC are degraded by the UPS (15-21). Conversely, induction of LD biogenesis (e.g. by growth of cells with oleate) results in stabilization of these proteins. While the UPS can control LD protein composition and regulate TAG lipolysis in LD, the mechanisms that target LD proteins for UPS-mediated degradation are not well understood.

Finally, emerging studies indicate that breakdown of LD constituents and LDs can occur by autophagy in response to cellular and environmental cues, and that this affects LD function in energy, lipid homeostasis, and ER protein quality control. Here, we discuss the process, mechanism, and consequences of LD autophagy, generally called lipophagy.

3. LIPOPHAGY: LD AUTOPHAGY

While the autophagy of various organelles was described as early as the 1960s, it was only recently that autophagy was implicated in the degradation of LDs (22). There are three main types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). As described below, all three forms of autophagy function in LD degradation.

3.1. Macrolipophagy

Macroautophagy is defined by the formation of an autophagosome, a double-membrane structure that surrounds and sequesters cytosolic components, and mediates fusion of the enveloped cargo with the lysosome (or vacuole in yeast) for degradation (Figure 1) (23). LD macrolipophagy was first described in mouse hepatocytes under conditions of starvation and lipid exposure (22). These studies revealed that exposure of hepatocytes to serum starvation results in co-localization of autophagosome and lysosome marker proteins with LDs and conversion of LC3-I to LC3-II, a vital step for initiating and lengthening autophagosomal membranes, at LDs. These studies also revealed that inhibition of macroautophagy, pharmacologically or by silencing of the autophagy machinery (ATG genes), leads to the accumulation of TAGs and LDs in serum-starved hepatocytes (22). Thus, nutrient limitation triggers LD degradation by macroautophagy in hepatocytes.

RAB7 and RAB10, members of the Rab GTPase family, have emerged as mediators of macrolipophagy in hepatocytes. RAB7 was originally identified as a regulator of late endosomes and autophagosome maturation (24-26). RAB10 has multiple roles in vesicular and membrane trafficking in adipocytes, epithelial cells and developing axons (27-29). Recent studies indicate that RAB7 and RAB10 accumulate on LDs in response to nutrient limitations.
and that activation of RAB7 and RAB10 is required to recruit autophagosome and lysosomal marker proteins to LDs. Conversely, depletion of either protein leads to LD accumulation in hepatocytes during starvation conditions (30, 31). Overall, these findings support the model that RAB7 and RAB10 play a role in the priming or licensing of LDs for macrolipophagy.

Recent findings also support a role for PLIN1 and PLIN2 in regulating LD macroautophagy. Stimulation of β-adrenergic receptors in 3T3-L1 cells activates PKA, and promotes recruitment of RAB7 to LDs and lipophagy. Knock-down of PLIN1 inhibits association of RAB7 and lysosomal marker proteins with LDs in activated 3T3-L1 cells (32). Similarly, PLIN2 deficiency reduces LD levels and enhances autophagic lipolysis in mouse liver and cultured hepatoma cells (33). In contrast, overexpression of PLIN2 protects hepatic lipid droplets from autophagic lipolysis. Thus, PLIN1 and PLIN2 may function as physical barriers that prevent recruitment of the macroautophagy machinery to LDs. Since PLIN1 and PLIN2 are targets for UPS degradation, it is possible that the UPS regulates LD function through effects on macrolipophagy. For a more extensive recent review of macrolipophagy see Schulze et al. (34).

### 3.2. CMA and lipophagy

CMA is a specialized form of autophagy that targets cytosolic proteins bearing the KFERQ degradation pentapeptide signal for lysosomal degradation (Figure 1) (35). Although CMA exclusively targets proteins and not lipids, several findings support a role for CMA in LD homeostasis. CMA is triggered by starvation, and mice with defects in liver CMA develop marked hepatosteatosis (36, 37). Moreover, PLIN2 and PLIN3 contain the KFERQ degradation pentapeptide and are CMA substrates (37). CMA-dependent degradation of PLIN2 and PLIN3 at the LD surface promotes the recruitment of a neutral lipid lipase (ATGL) and macroautophagy machinery components to the LD. Conversely, impairment of CMA or mutations in the pentapeptide signal of PLIN2 or PLIN3 prevents association of ATG core proteins with LDs and promotes LD accumulation (37). Overall, these findings indicate that CMA-mediated degradation of PLIN2 and PLIN3 stimulates lipolysis and macrolipophagy by promoting the recruitment of lipases and macrolipophagy machinery components to LDs.

### 3.3. Microlipophagy

In yeast, LDs are also degraded by microautophagy. In microlipophagy, LDs are not enveloped by autophagosomes, but are delivered directly to the vacuole (the yeast lysosome). Microlipophagy has been detected in yeast in response to nitrogen starvation, glucose depletion, survival during stationary phase, and phospholipid imbalance. Under these conditions, LDs are taken up into the vacuole at sites of vacuolar membrane invagination (Figure 1) (38-41). However, different environmental conditions stimulate different mechanisms for microlipophagy.

#### 3.3.1. LD-vacuolar contact sites during ATG core gene dependent microlipophagy

In nitrogen starvation- and stationary phase-induced microlipophagy, LDs bind to specific sterol-rich, raft-like liquid ordered (L_0) vacuolar microdomains (38, 39). Recent studies support a role for two essential Niemann-Pick type C (NPC) sterol transporter proteins, Ncr1p and Npc2p, in L_0 microdomain formation under both conditions (42). These proteins are internalized into the vacuolar lumen, where they transfer sterols to the vacuolar membrane. If these proteins are absent or fail to localize to the vacuolar lumen, the formation and expansion of L_0 microdomains needed for microlipophagy is severely affected.

Interestingly, the source for sterols in L_0 microdomains differs in yeast in stationary phase and undergoing nitrogen starvation. Sterol-rich intraluminal vesicles (ILVs) are the main source of L_0 microdomain sterols in nitrogen starved yeast (42). These ILVs are transported to the vacuole by multivesicular bodies (MVBs), membrane bound structures that are generated from late endosomes, contain internal membranes and deliver proteins and lipids to the vacuole (43). In contrast, sterol esters in LD are the sterol source in stationary phase yeast cells (39). Interestingly, there are reciprocal interactions between microlipophagy and these sterol-rich microdomains in stationary phase yeast. Vacuolar microdomains are required for microlipophagy (39). Conversely, microlipophagy is essential to maintain the L_0 microdomains, potentially because LDs that are taken up into the vacuole by microlipophagy are a major source for sterol esters for vacuolar L_0 microdomains (44).

Finally, core ATG genes, which encode proteins that mediate autophagosome formation, are required for microlipophagy in both stationary phase and nitrogen starved yeast (38, 39, 42). However, the mechanism of ATG gene function varies under these two conditions. ATG genes are required for localization of NPC proteins to the vacuole in stationary phase cells. Specifically, deletion of ATG1, 2, 3, 5, 7, 8, or 18 results in accumulation of Ncr1p and Npc2p as punctate, presumably aggregated structures in the cytosol (42). Surprisingly, under conditions of nitrogen starvation, localization of Ncr1p, Npc2p, or ILVs to the vacuole is not affected in ATG mutants. Rather, ATG genes are required for autophagosome-mediated delivery of sphingolipids, another vital component of the L_0 microdomains, to the vacuole (45, 46).
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Currently, it is not clear whether Ncr1p, Npc2p, or ILV-dependent sterols are required for microlipophagy under conditions of acute glucose depletion. However, microlipophagy in glucose-depleted yeast requires ATG core genes including Atg14p, an autophagy-specific subunit of phosphatidylinositol 3-kinase complex I that localizes to Lₜ microdomains (41). Moreover, ATG14 is required for Lₜ formation and microlipophagy, and localization of Atg14p to Lₜ sites is dependent upon the AMPK pathway for energy sensing during acute glucose depletion. The defect in microlipophagy observed in glucose-depleted atg14Δ cells does not appear to be due to effects on macroautophagy: ATG14 is required for macroautophagy in fed yeast cells but not in yeast undergoing acute glucose depletion (41). This finding suggests an unexpected plasticity in autophagy in response to different cellular cues and a novel function of Atg14p in microlipophagy.

3.3.2. ATG core gene-independent forms of microlipophagy

Microlipophagy that does not require core ATG genes has been observed in yeast under two conditions: lipid imbalance produced by defects in PC biosynthesis (47), and transition through the diauxic shift, the shift from glycolysis- to respiration-driven growth when glucose becomes limiting (48). Since core ATG genes are required for Lₜ microdomain formation (42), it is possible that LD uptake into vacuoles does not occur at Lₜ microdomains in ATG-independent forms of microautophagy. Alternatively, Lₜ microdomains may function in all forms of microlipophagy; however, generation of those subdomains may occur by different mechanisms.

Interestingly, both forms of ATG gene-independent microlipophagy require the endosome sorting complexes required for transport (ESCRT) machinery, conserved membrane complexes that mediate invagination of late endosomal membranes to produce MVBs (49). Since MVBs transport hydrolases and other macromolecules to the vacuole, ESCRT affects micro- and macroautophagy through effects on vacuolar biogenesis. However, emerging evidence supports a direct role for the ESCRT in vacuolar membrane remodeling in ATG gene-independent microlipophagy.

Lipid imbalance-induced microlipophagy requires Vps4p, which mediates ESCRT III disassembly, and Esm1p/Atg39p, a newly identified class V ESCRT protein that has also been implicated in nucleophagy (40, 50). Microautophagy of cargos including LDs in post-diauxic yeast requires multiple ESCRT components, including Vps27p, a clathrin- and ubiquitin-binding protein and component of the ESCRT-0 complex normally responsible for initiating the MVB pathway (49). Indeed, passage through the diauxic shift results in relocalization of Vps27p from endosomes to punctate structures on the vacuolar membrane. The clathrin-binding domain of Vps27p is not required for its relocalization to the vacuole after the diauxic shift. However, it is required for efficient microlipophagy under these conditions. Other studies confirm that ESCRT can function directly on the vacuolar membrane to sort and direct polyubiquitinated protein cargo into the vacuolar lumen for degradation (51). These findings raise the possibility that ESCRT mediates invagination of the vacuolar membrane for LD uptake during microlipophagy in yeast after the diauxic shift, and potentially also in yeast exposed to lipid stress.

4. FUNCTIONS OF LIPOPHAGY

4.1. Energy mobilization

A role for lipophagy in release of free fatty acids (FFAs) from LDs for energy mobilization in response to starvation was first identified in mouse hepatocytes (22). Other studies revealed a role for lipophagy in starvation-induced FFA release in the proximal tubule of the kidney (52), hypothalamic and primary striatal neurons, glial cells, lymphocytes, macrophages, cultured adipocytes, gastrointestinal epithelial cells, and prostate cancer cells (53). Lipophagy in response to nutrient limitation is also observed in the yeast *Saccharomyces cerevisiae*, the nematode *Caenorhabditis elegans*, and the fungus *Fusarium graminearum* (53). Finally, lipophagy can be activated in brown adipose tissue by cold shock, where it promotes the release of FFAs from brown fat to supply peripheral tissues with energy and promote their survival during cold stress (54). Thus, lipophagy is an established mechanism to supply energy to cells under various metabolic demands.

As described above, starvation-induced LD degradation occurs by macroautophagy in mouse liver (22). In contrast, yeast subjected to nitrogen starvation or acute glucose limitation degrade LDs by microlipophagy (38, 41). Since deletion of cytosolic neutral lipid lipases does not have severe effects on survival of yeast in stationary phase, microlipophagy may also be a major pathway for TAG metabolism during that stage of the yeast life cycle (55-57). Yet to be determined is why different cell types use different mechanisms for microlipophagy.

Although lipolysis can be used to release FFAs from LDs, lipophagy may be activated during starvation in some cell types because it allows for rapid release of FFAs. Moreover, use of lipophagy as opposed to lipolysis for energy mobilization from LDs varies among tissues. Lipolysis is the primary mechanism for FFA release from LDs in white adipose
tissue, which expresses high levels of HSL and ATGL (12, 58-61). In contrast, lipophagy appears to be the major mechanism for FFA mobilization in liver, which expresses low levels of HSL and ATGL (13). Elevated FFA results in lipotoxicity, elevated reactive oxygen species production, uncoupling of mitochondria, apoptosis, and insulin resistance (62-65). Therefore, use of the relatively slower process of lipolysis for FFA release in white adipose tissue may protect against release of excessive levels of FFA from the large stores of TAGs in those cells.

4.2. Lipid homeostasis

The function of lipophagy in lipid regulation extends beyond TAG storage and FFA release. Lipophagy is a mechanism to protect cells from excess intracellular lipids and lipotoxicity. Up-regulation of macrolipophagy was first detected in hepatocytes exposed to high levels of oleic acid (22). Subsequent studies showed that lipid overload can increase autophagy in cells including neurons, beta cells, myocytes and epithelial cells (66-70). Conversely, blocking autophagy in cultured myocytes leads to elevated TG levels and cell death as a result of lipid overload (71). Thus, lipophagy protects cells from lipotoxicity by removal of excess intracellular lipids.

Lipophagy also protects yeast from lipid stress produced by inhibition of PC biosynthesis (40). The immediate response to inhibition of PC biosynthesis is altered levels of phospholipids, decreased growth rates, and defects in the morphology and distribution of mitochondria and ER, the two organelles where PC biosynthesis occurs. Surprisingly, yeast adapt to this lipid stress: their growth rates, ER and mitochondrial morphology and distribution, and levels of many phospholipids are restored (40). We found that TAG and sterol ester levels as well as LD biogenesis and degradation by microlipophagy are increased in cells that have adapted to this lipid stress. Moreover, we find that mutations that block TAG and LD biosynthesis or microlipophagy severely inhibit adaptation. These studies support the model that excess lipids are stored in LDs in the form of TAG and degradation of those lipids by microlipophagy protects yeast cells from lipid imbalance.

Finally, lipophagy has also been implicated in protecting cells from excess cholesterol. Reverse cholesterol transport, transport of free cholesterol from macrophage foam cells in atherosclerotic plaques to the liver where it is excreted in bile, is one mechanism to reduce cholesterol levels (72). Recent studies indicate that lysosomes contribute to lipid breakdown in lipid-loaded macrophage foam cells (73). These studies also revealed co-localization of autophagosome and lysosome marker proteins with LDs, conversion of LC3-I to LC3-II in subcellular fractions enriched in LDs, and a role for lysosomal acid lipases in release of free cholesterol from cholesterol esters in LDs in macrophage foam cells. Thus, LD breakdown in lipid-loaded macrophage foam cells occurs by macroautophagy. Recently, these studies showed that lipophagy is required for release of free cholesterol from cholesterol esters in LDs and reverse cholesterol transport from lipid-loaded macrophage foam cells in culture and in whole animals (73). Thus, lipophagy may contribute to clearance of excess cholesterol from peripheral tissues and be a target for treatment of atherosclerosis (74).

4.3. Protein quality control

LDs have also emerged as cellular “protein sinks.” LDs sequester histones H2A and H2B during oogenesis in Drosophila (75). Defects in this process results in toxic accumulation of histones, which leads to mitotic error and apoptosis (76, 77). LDs also sequester misfolded cytosolic proteins and prevent them from forming toxic aggregates under several pathological states and conditions (78, 79). Finally, LDs have been implicated in the assembly of hepatitis C virus (HCV) and in liver steatosis caused by HCV infection. Specifically, two HCV core proteins localize to LDs where they contribute to transfer of lipids from LDs to the developing virion during virus assembly (80-82).

Our group has recently identified a novel role for LD and lipophagy in ER proteostasis under conditions of lipid imbalance. Lipid imbalance produced by defects in PC biosynthesis results in accumulation of unfolded proteins in the ER (ER stress) and activation of the unfolded protein response (UPR) (40), a signal transduction pathway that down-regulates protein synthesis and up-regulates proteostasis mechanisms in response to ER stress (83). One pathway that is activated by the UPR is ER-associated protein degradation (ERAD), a pathway for retrotranslocation of unfolded ER proteins to the surface of the organelle, where they are ubiquitinated and targeted for degradation by the proteasome (84, 85).

LD biogenesis and microautophagy have emerged as an ERAD-independent mechanism for ER proteostasis in yeast undergoing acute lipid imbalance. Specifically, polyubiquitinated proteins and Kar2p, the yeast homologue of the ER chaperone BiP, are enriched in LDs isolated from yeast undergoing lipid stress (40). Furthermore, these LDs are targeted to the vacuole for degradation by microautophagy. As described above, lipid stress induced microlipophagy does not require the core autophagy gene ATG7, but does require ESCRT components. Finally,
microlipophagy is essential for yeast cell survival during lipid stress (40).

These findings support a novel mechanism for ER proteostasis in response to lipid stress whereby LDs remove unfolded proteins from the ER and target them for degradation by lipophagy. They also provide support for the model that LDs function as "escape hatches" in ER quality control (86). Interestingly, LDs may also remove damaged proteins from mitochondria in yeast (87). Under conditions of stress, specific damaged mitochondrial outer membrane proteins associate with LDs, which in turn are degraded by lipophagy. Therefore, LDs may serve as a vehicle for segregation and degradation of damaged proteins from different compartments.

5. CONCLUSION

It is now clear that LD autophagy occurs and contributes to established and newly identified LD functions in energy and lipid homeostasis and ER proteostasis. However, there are fundamental questions that remain unresolved. Indeed, lysosomes can be 100 to 1000 times smaller than LDs in mammalian cells. In light of this, it is not clear how LDs can be taken up into lysosomes. Are there mechanisms for fragmentation of LDs that are targeted for autophagic degradation?

Studies from multiple groups revealed that macrolipophagy and microlipophagy are used to release of FFAs from LDs. However, why different cell types use different autophagy mechanisms and how those mechanisms are regulated are not well understood. Indeed, although macroautophagy has been studied extensively, our understanding of microautophagy and microlipophagy are limited. Nonetheless, available evidence indicates that microlipophagy is complex. There appears to be multiple forms of microlipophagy in yeast that are induced by different conditions, rely upon or do not rely upon core ATG genes, and utilize different mechanisms for generating docking sites for LDs on the vacuole. Future studies will reveal the precise mechanism underlying these pathways, how they are regulated and whether they are conserved in other cell types.

Finally, recent studies on microlipophagy have revealed novel mechanisms including a possible role for the ESCRT machinery in invagination of the vacuolar membrane for LD uptake and a role for LD biogenesis and microlipophagy in ER proteostasis. Ongoing and future studies will reveal whether ESCRT mediates lyosomal membrane invagination during microlipophagy in metazoans, other possible targets for ESCRT function in membrane curvature, whether LDs regulate ER proteins quality control in metazoans, the targets for ER proteostasis by LDs, and whether LDs control the quality of other organelles and cellular compartments.

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**Abbreviations:** LD, lipid droplet; FFA, free fatty acid; ER, endoplasmic reticulum; TAG, triacylglycerol; SE, sterol esters; AMPK, 5-AMP activated protein kinase; PKA, cAMP-dependent protein kinase; ATGL, adipose triglyceride lipase; HSL, hormone sensitive lipase; UPS, ubiquitin-proteasome system; CMA, chaperone mediated autophagy; PC, phosphatidylcholine; NPC, Niemann-Pick type C; ILV, intraluminal vesicle; MVB, multivesicular bodies; ESCRT, endosome sorting complexes required for transport; HCV, hepatitis C virus; UPR, unfolded protein response; ERAD, endoplasmic reticulum associated degradation

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