Published in final edited form as:

Curr Opin Lipidol. 2018 June ; 29(3): 203–211. doi:10.1097/MOL.0000000000000509.

Classical and alternative roles for autophagy in lipid metabolism

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Abstract

Purpose of review—Intracellular lipid metabolism is a complex interplay of exogenous lipid handling, trafficking, storage, lipolysis, and export. Recent work has implicated the cellular degradative process called autophagy in several aspects of lipid metabolism. We will discuss both the classical and novel roles of autophagy and the autophagic machinery in this setting.

Recent findings—The delivery of lipid droplets to lysosomes for hydrolysis, named lipophagy, was the first described functional role for autophagy in lipid metabolism. The molecular machinery and regulation of this selective form of macroautophagy is beginning to be discovered and has the potential to shed enormous light on intracellular lipolysis. Yet, the autophagic machinery appears to also be coopted for alternative roles that include interaction with cytosolic lipolysis pathways, supply and expansion of lipid droplets, and lipoprotein trafficking. Additionally, lesser studied forms of autophagy called microautophagy and chaperone-mediated autophagy have distinct roles in lipid handling that also intersect with classical macroautophagy. The integration of current knowledge in these areas into a holistic understanding of intracellular lipid metabolism will be a goal of this review.

Summary—As the field of autophagy has evolved and expanded to include functional roles in various aspects of cellular degradation, so has its role in intracellular lipid metabolism. Understanding the mechanisms underlying these classical and alternative roles of autophagy will not only enhance our knowledge in lipid biology but also provide new avenues of translation to human lipid disorders.

Keywords

autophagy; lipid droplet; lipid metabolism; lipolysis; lipophagy; lipoprotein

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION TO INTRACELLULAR LIPOLYSIS

Intracellular lipids take diverse forms purposed toward essential structural, signaling, and metabolic goals. However, inappropriate trafficking and buildup of lipids such as free fatty acids (FFA), free cholesterol, and derivatives can be highly toxic to cells and drive cardiometabolic disease pathology. The lipid droplet is a dynamic organelle coated with hundreds of proteins regulating lipid flux where FFA and free cholesterol are stably stored as triglycerides or cholesteryl esters, respectively. In turn, scenarios requiring lipid release drive lipolysis, the catabolism of triglycerides to yield glycerol and FFA or cholesteryl esters to yield free cholesterol and FFA. Other forms of lipolysis take prominence in the gut and vasculature, but intracellular lipolysis is the main process releasing FFA and free cholesterol from cytoplasmic lipid droplets and can be further divided into two types. Cytosolic lipolysis occurs at neutral pH and is mediated by a series of lipases including adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoacylglycerol lipase for triglycerides [1], or a number of candidate hydrolases for cholesteryl esters. Classically, physiological regulation of cytosolic lipolysis is modulated by catecholamines, hormones, and growth factors which commonly act on cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA) signaling to control lipase activity [2,3]. Lysosomal lipolysis occurs at acidic pH in the lysosome and primarily involves lysosomal acid lipase-mediated degradation of endocytically derived lipids [4]. A major discovery in the field of lipolysis was the realization that autophagy, an intracellular catabolic pathway, is also utilized to deliver lipid droplets as cargo to the lysosome [5]. In this review, we focus on recent developments in understanding the regulation and molecular machinery of lipophagy, the autophagic delivery of lipid droplets to the lysosome for lipolysis. Further, we highlight a growing body of work showing novel, alternative roles for autophagy in regulating lipid metabolism and lipolysis in ways that are quite distinct from canonical lipophagy.

AUTOPHAGY: SELF-EATING FOR CLEARANCE AND RENEWAL

Along with the ubiquitin-proteasome system, autophagy is the primary degradative process used by cells for clearance and degradation of cytoplasmic contents [6]. All forms of autophagy rely on delivery of cargo to the lysosome, where a low-pH environment and an array of acid hydrolases degrade contents to basic components for subsequent use in anabolic reactions. To date, three major forms of autophagy are recognized: macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy [7] (Fig. 1).

Among these, macroautophagy is the best characterized and involves formation of double membrane vesicles called autophagosomes for sequestration of cellular components. Autophagosomes then fuse with lysosomes for cargo delivery and acid hydrolysis of contents. A growing series of over 30 autophagy-related (ATG) genes mediate different aspects of autophagy, including nucleation, orientation, and elongation of the double membrane or its subsequent fusion with lysosomes [8]. Second, CMA uses the heat-shock cognate protein 70 (Hsc70) as a chaperone to recognize the linear peptide sequence KFERQ within specific target proteins to transport them directly into the lysosomal lumen by binding to the lysosome-associated membrane protein 2a [9]. Finally, microautophagy is thus far the

least investigated form of autophagy and involves direct invagination of the lysosomal membrane for engulfment of target cargo [10].

LIPOPHAGY – THE BRIDGE LINKING AUTOPHAGY AND INTRACELLULAR LIPOLYSIS

In 2009, Singh *et al.* [5] observed that lipid droplets and autophagic membrane components associate during nutrient deprivation and that inhibition of macroautophagy increases triglyceride storage in lipid droplets. The net implication of this study was that autophagosomes were capable of selectively sequestering lipid droplets for delivery to lysosomes for lipolysis in fibroblasts and hepatocytes. This process was named ‘Lipophagy’ and has subsequently been characterized in dozens of settings, including neurons [11], macrophages [12], and adipocytes [13]. Subsequent studies have also emphasized that lipophagy is not only important for triglyceride metabolism but also cholesterol catabolism and efflux in cell types such as macrophages [14]. Thus, the field has begun to investigate key questions regarding the mechanisms and roles of lipophagy in overall lipolysis. These include first determining the molecular machinery allowing autophagosome interaction with the lipid droplet and how these mediators are recruited and regulated. It is also of great interest to characterize the physiological and signal transduction mechanisms regulating lipophagy to meet lipolytic demands. Examination of these questions frames lipophagy as an underexplored but important contributor to lipolysis in many states.

MOLECULAR MACHINERY OF LIPOPHAGY: IDENTIFICATION AND INDUCTION

In the purest conceptual sense, lipophagy is a form of selective autophagy, defined as an autophagic process for which there is favored and regulated selection of certain cargo with kinetics distinct from nonselective ‘bulk’ autophagy. The canonical molecular basis for selective macroautophagy features linking of tagged cargo to the autophagosome via adapter proteins [15]. Thus, it is of great interest to determine how lipid droplets might be tagged to recruit autophagosomes, which proteins are relevant adapters, and more broadly, how this physical interaction is otherwise initiated and regulated.

Ubiquitination and selective autophagy adapters

Sequestosome-1/p62 is a critical selective autophagy adapter binding polyubiquitinated proteins through its C-terminal Ubiquitin-associated domain [16]. During selective autophagy, it serves as an adapter between polyubiquitinated cargo and the autophagosome coat protein light chain 3 (LC3) [15]. One possible mechanism for lipid droplet ubiquitination is via ancient ubiquitously expressed protein 1, a highly expressed lipid droplet protein able to recruit the ubiquitin conjugating enzyme E2 G2 [17], though a clear link to subsequent autophagic degradation is uncertain. A separate study reveals rapamycin-driven autophagy promotes localization of p62 on lipid droplets via interaction with perilipin 2 (PLIN2), a lipid droplet membrane protein. The recruitment of p62 to lipid droplets decreases lipid accumulation in myocytes efficiently, suggesting that p62 may direct autophagosomes to the lipid droplets and accelerate lipid turnover by lipophagy [18].

Interestingly, mutations in the protein huntingtin which associates with organelle membranes lead to accumulation of dysfunctional autophagosomes as well as cytoplasmic lipid droplets in multiple cell types [19]. It is suggested that such changes in huntingtin may lead to a defective association with p62 and hinder the recognition of lipid droplets by autophagosomes. However, there is an overall paucity of evidence for ubiquitination and classic selective autophagy adapter proteins serving major roles in lipophagy, in contrast with their well established roles in clearance of other selective autophagy cargo [15].

Rab GTPase's

The Rab family of small GTPases are well known to mediate cellular trafficking events. Rab7 was the first member of this family to be implicated in lipophagy and associates with lipid droplets, autophagic membranes, and lysosomes under starvation conditions. Silencing Rab7 expression or reducing its activity leads to accumulation of lipid droplets in cultured liver cells [20]. A second member of this family, Rab10, also localizes to lipid droplets and autophagosomes during starvation in a Rab7-dependent manner. A recent study demonstrated Rab10 then recruits an EHBP1-EHD2 complex to initiate lipophagy (Fig. 2). EHBP1 serves as an adapter protein for recruiting EHD2, a dynamin-like ATPase that could mechanically drive the extension of the autophagosome membrane around the lipid droplet for engulfment [21[■]]. Other Rabs, such as Rab8, Rab18, Rab25, Rab32, are also found at lipid droplets and may contribute to lipophagy, although specific molecular mechanisms remain unclear and call for further investigation [22,23].

Microlipophagy

An intriguing new mechanism potentially mediating lipophagy is direct engulfment of lipid droplets by the endosome or lysosome, termed microlipophagy (Fig. 2). A series of studies in yeast has spearheaded investigation into this phenomenon, and many of the key molecular players have clear mammalian homologues. First, Wang *et al.* [24] found that during gradual nutrient depletion, yeast undergo microautophagy-mediated internalization of lipid droplets directly into a lysosome-like vacuole. This process relied on the core autophagy genes ATG21 and ATG32, along with formation of sterol-enriched liquid-ordered microdomains at sites of engulfment. These microdomains give the vacuole a 'golf ball-like' appearance with liquid ordered forming concave indentations thought to favor cargo entry. In turn, lipid products generated by microlipophagy supply these microdomains [24] and a subsequent study found the lysosomal cholesterol transport proteins Niemann-Pick C 1/2 to be necessary for their formation and overall microlipophagy [25[■]]. Other work found that the autophagy gene ATG14p translocates to vacuole liquid ordered upon acute glucose starvation and along with ATG6p is required for microlipophagy and liquid-ordered formation [26[■]]. Finally, a role for the cellular endosomal sorting complexes required for transport membrane budding and remodeling machinery has been found in completing the engulfment of lipid droplets during nutrient depletion [27] or phospholipid imbalance [28]. Further investigation into microlipophagy and its relevance to lipid turnover in mammalian cells is a promising area of future study.

REGULATION OF LIPOPHAGY

Induction of lipophagy is part of a complex cellular and physiological response to several stimuli such as starvation [5], β -adrenergic stimulation [29], fatty acid loading [5], and cold exposure [30[■]]. Accordingly, negative (Fig. 3A) and positive (Fig. 3B) regulation of lipophagy seems to be well integrated with, and responsive to, many of the factors regulating autophagy and lipolysis, including classic stress and nutrient-responsive pathways. One such example is the mammalian target of rapamycin (mTOR) pathway. During conditions of high nutrient availability, the cytoplasmic mTOR complex 1 (mTORC1) is recruited to and activated on the surface of lysosomes [31] where it phosphorylates and inhibits key autophagy factors, including ULK1, ATG13, AMBRA1, ATG14L, and transcription factor EB (TFEB) [32]. Conversely, starvation inactivates and releases mTORC1 from lysosomes, allowing activity of downstream autophagy targets [33]. Though mTOR inhibition is not a very specific way to enhance lipophagy, it has been shown to do so *in-vivo* in several contexts. Martinez-Lopez *et al.* [30[■]] showed induction of lipophagy specifically in the brain with rapamycin reduced lipid accumulation in an autophagy-dependent fashion. Remarkably, using rapamycin to drive lipophagy or ATG7 silencing to block lipophagy was sufficient to drive efferent neural signaling to induce matching lipophagic responses in brown adipose tissue and liver. Thus, lipophagy occurs intrinsically in the central nervous system, can be modulated by mTOR signaling, and is a key driver of secondary lipophagy in the brown adipose tissue and liver [34]. More broadly, decreased mTOR signaling appears to be frequently associated with physiological states which lead to increased lipophagy.

A second primary cellular energy sensing pathway with major influence on autophagy and lipophagy is adenosine monophosphate-activated protein kinase (AMPK) signaling. During starvation, AMPK can activate autophagy through numerous mechanisms, including phosphorylation of the key autophagy kinase Ulk1, activation of Sirtuin 1 (SIRT1), and inhibition of mTOR [35]. Further, AMPK is the crucial sensor activating ATG14p-mediated microlipophagy during glucose deprivation in yeast [26[■]]. Regulation of lipophagy is also intertwined with that of cytosolic lipolysis, classically known to be mediated by β -adrenergic stimulation and cAMP/PKA/cAMP response-element binding protein (CREB) signaling (Fig. 3). β adrenergic stimulated lipolysis in adipocytes is partially dependent on intact Rab7-mediated lipophagy [29]

Autophagy and lipophagy are also under major transcriptional control. The most notable positive effectors of this process are the melanogenesis-associated-TFE family of transcription factors (Fig. 3A) [36,37]. Members of this family including TFEB or TFE3 can both induce lipophagy and reduce hepatic lipid accumulation. In contrast, the absence of either TFEB or TFE3 increases lipid accumulation [38,39]. TFEB/TFE3 also target the peroxisome proliferator-activated receptors (PPAR) and PPAR-gamma coactivator-1 family of transcription factors and coactivators. These assist in driving transcription of mitochondrial and fatty acid oxidation genes allowing full utilization of the fatty acid products of lipophagy [38,39]. Two other recent studies identified farnesoid-X receptor (FXR) as a transcriptional repressor of autophagy (Fig. 3B). During fasting, the transcription factors PPAR α and CREB compete with and overcome FXR binding to upregulate autophagy. Correspondingly, lipophagy is inhibited by FXR and enhanced by CREB and

PPAR α [40,41]. Last, the forkhead box-O (FOXO) family of transcription factors has classically been linked to regulation of autophagy via control of autophagy gene expression. Lettieri Barbato *et al.* [13] found that metformin, an AMPK-activating drug, and nutrient restriction drive FOXO1 mediated increases in lipophagy and lysosomal acid lipase expression in adipocytes. Similarly, FOXO is a major regulator of autophagy genes notably including ATG14 in liver. FOXO silencing markedly impairs lipophagy, whereas ATG14 overexpression is sufficient to drive it [42]. Beyond transcription factors, a recent study has identified a mechanism for epigenetic repression of lipophagy. In the fed state, small heterodimer partner recruits the lysine-specific histone demethylase 1 (LSD1) to repress CREB-targeted autophagy genes (Fig. 3A). Small heterodimer partner or LSD1 knockout both markedly increase hepatic autophagy and reduce lipid accumulation [43]. Taken together, these transcriptional and signal transduction mechanisms construct an intricate regulatory network controlling lipophagy.

ALTERNATIVE FUNCTIONS OF AUTOPHAGY MACHINERY IN LIPID METABOLISM

In recent years, it has become clear that straightforward degradative lipophagy is only one of many junctures where autophagy and lipid metabolism intersect and that the impact of autophagy deficiency is remarkably pleiotropic in this regard. Novel, alternative roles for autophagy include modulation of lipid droplet surface proteins, physical interaction with the cytosolic lipolysis machinery, supplying rather than depleting lipid droplets, and lipoprotein trafficking (Fig. 4a–d). Perhaps most importantly, this body of work urges reinterpretation of earlier studies which drew simplified dichotomies between cytosolic lipolysis and lipophagy and of their commonly employed methods of assessing lipophagy.

Chaperone-mediated autophagy initiates degradation of lipid droplet surface proteins

Perilipins (PLIN's) are a class of proteins coating the lipid droplet surface and serve as a major point of control for both lipophagy and lipolysis by physically blocking access to the triglyceride and cholesteryl ester-rich core. CMA plays an unexpected indirect role in lipolysis by mediating degradation of the PLIN2 and 3 (Fig. 4a). Both PLIN2 and 3 bear KFERQ-like peptide motifs necessary for hsc70 binding and translocation into the lysosome, and mutation of these motifs leads to perilipin accumulation and reductions in both lipophagy and cytosolic lipolysis [44]. A follow-up study identified that hsc70 recognition of PLIN2/3 precedes an AMPK-mediated phosphorylation that may facilitate PLIN release for degradation [45]. Given that a large fraction of the cellular proteome is thought to be amenable to CMA-mediated degradation, future studies may find any number of lipid droplet and lipolysis proteins to be regulated by CMA.

Lipophagy and cytosolic lipolysis interact

Microtubule associated protein 1 LC3 is an ATG8 family protein that coats the autophagosome and is lipidated during autophagosome maturation. Many other modes of selective autophagy rely on LC3-interacting region (LIR) motifs present on adapter proteins, such as p62, for conjugation to cargo. A recent study found that the classic cytosolic lipases ATGL and HSL contain several putative LIR motifs, coimmunoprecipitate with LC3, and

likely dock on the cytoplasmic surface of autophagosomes (Fig. 4b, [30[■]]). Mutation of a single LIR in ATGL was sufficient to totally disrupt ATGL trafficking to the lipid droplet, suggesting the interaction with LC3 may be important for neutral lipolysis. However, it was not determined whether this disruption was specific to interaction with LC3 and the function of LIR motifs in HSL is still uncertain. Overall, the apparent requirement for LC3 presence at the lipid droplet for neutral lipolysis suggests cooperativity between these two lipolytic systems. A major question in lipophagy is how and whether the modestly sized autophagosome engulfs much larger lipid droplets. One possibility is that the autophagosome recruits cytosolic lipases to deplete large lipid droplets until total engulfment is achievable. LC3 and autophagosomes may also function at the lipid droplet by serving as a scaffold for MEK-ERK kinases, key regulators of lipolysis [46] (Fig. 4b). Finally, ATGL was recently shown to markedly influence autophagy through SIRT1-dependent transcriptional regulation [47[■]]. Particularly remarkable is that in hepatocytes, the increase in lipophagy driven by ATGL overexpression seemed to be far more relevant to fatty acid liberation than ATGL activity itself. In aggregate, these studies suggest remarkable code-pendence of lipophagy and neutral lipolysis, and that many earlier estimates of their relative contributions are overly simplistic.

Autophagy supplies lipid droplets

The concept of autophagy as a primarily catabolic pathway for lipid droplets has dominated the field from the start. However, several lines of evidence now question the universality of this concept and instead suggest fundamental roles for autophagy in lipid droplet anabolism (Fig. 4c). First, an increasing number of studies now support that autophagy deficiency actually reduces lipid droplet accumulation *in vitro* and *in vivo* both during hepatic fasting [48–50] and in several other contexts such as adipogenesis [51,52]. Experimental considerations concerning the degree of prior lipid loading and the type and duration of starvation may explain these apparent divergences in the net role of autophagy [5,20]. Additionally, there is a glaring disconnect between the clear induction of autophagy in the liver during short-term fasting versus the robust accumulation of lipid. Of course, this is partially driven by adipose tissue lipolysis and hepatic uptake, but a growing body of work characterizes new roles for autophagy in lipid droplet anabolism. During starvation, bulk autophagic breakdown of membranous organelles is known to be a major cell-autonomous source of cellular lipids (Fig. 4c). Using fluorescently labeled fatty acids, Rambold *et al.* [53[■]] recently demonstrated that fatty acids fluxing through this pathway are first delivered from the lysosome to lipid droplets for cytosolic lipolysis, yielding FFAs to be oxidized by adjacent mitochondria. A second study showed that amino acid starvation is sufficient to markedly induce the accumulation of lipid droplets in an autophagy-dependent manner [54[■]]. Activation of AMPK or blocking mTORC1 through several means markedly impaired lipid droplet biogenesis. diacylglycerol O-acyltransferase 1 (DGAT1), a terminal enzyme in triglyceride synthesis, was shown to be essential for trafficking the products of starvation-induced lysosomal lipolysis into lipid droplets, thereby protecting against mitochondrial lipotoxicity [54[■]]. These studies also draw attention to the lack of knowledge regarding how lysosomes transfer liberated fatty acids to lipid droplets. Overall, a plurality of studies now suggest a predominant role for autophagy in lipid droplet anabolism and exemplify how

autophagy deficiency can impair lipid oxidation in a way that is completely unrelated to lipophagy.

Autophagy participates in lipoprotein trafficking

Classically, hepatocytes form and secrete lipoproteins for systemic lipid delivery. Apolipoprotein B (ApoB) forms the core of LDL and is subject to oxidative modification and aggregation prior to secretion (Fig. 4d). Remarkably, autophagy targets ApoB aggregates for degradation to greatly limit secretion of dysfunctional LDL [55]. The transmembrane receptor sorting protein sortilin was also recently discovered to bind ApoB and target it for autophagic degradation, resulting in reduced LDL secretion. This may be one mechanism by which a known genetic polymorphism increasing sortilin expression substantially lowers circulating LDL levels [56]. At the receiving end, lipoproteins are endocytosed in some cell types including macrophages for subsequent lysosomal hydrolysis. Sortilin also mediates LDL uptake in macrophages [57], and it would be interesting to examine similar interactions with autophagy in this context. In endothelial cells, LDL can be found within autophagosomes, and autophagy deficiency results in LDL accumulation suggesting an important role for autophagy in LDL trafficking to the lysosome. This potential role for autophagy in LDL trafficking may relate to LC3-associated phagocytosis, a noncanonical role for autophagy in which autophagy proteins are coopted for membrane trafficking of endocytic cargo [58]. Together, these studies suggest the versatile machinery of autophagy intersects with secretory and endocytic mechanisms to modulate lipoprotein trafficking in multiple contexts.

CONCLUSION

Recent progress has increasingly defined the molecular mechanisms and regulation of lipophagy, and characterized additional functions of autophagy, including modulation of lipid droplet surface proteins, interactions with cytosolic lipolysis, lipid droplet anabolism, and lipoprotein trafficking. Though the field is young, we believe significant future progress in this field relies on several key factors. First, there is still a glaring lack of knowledge regarding the molecular mechanisms directly mediating interactions between the lipid droplet and autophagosomes or lysosomes. Finding the key proteins and membrane features specific to this process is not only intrinsically informative but also will allow more rigorous characterization of its broader roles in cell biology and physiology. Second, there is a great need for rigor and consensus in defining which assays and interpretations thereof truly represent lipophagy and/or alternative roles of autophagy in lipid metabolism. For example, it is clear from the many studies summarized in this review that the mere presence of LC3 at the lipid droplet is far from sufficient to conclude that degradative lipophagy is occurring. Experimental approaches and interpretations should consider whether a given perturbation will result in lipid accumulation or depletion, the type of autophagy that may be involved, and whether lipophagy or cytosolic lipases directly mediate lipolysis. Overall, continued study of lipophagy and alternative roles for autophagy in lipid metabolism is a fascinating area with enormous implications for understanding cell biology, physiology, and human disease.

Acknowledgments

We would like to acknowledge the excellent contributions of many additional scholars in this field, which could not be discussed for space limitations.

Financial support and sponsorship

The work was supported by grants from National Institutes of Health (R01 HL125838 and P30 DK020579), the US Department of Veterans Affairs (VA MERIT I01 BX003415), and the American Diabetes Association (Innovative Basic Science 1–18-IBS-029) to B.R., and National Institutes of Health (F31 HL132434) to T.D.E.

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KEY POINTS

- Early work has begun to define the molecular mechanisms directly mediating interactions between autophagosomes and lipid droplets.
- Regulation of lipophagy involves transcriptional, epigenetic, and posttranslational control and overlaps much with regulation of neutral lipolysis and autophagy.
- Roles for autophagy in lipid metabolism extend far beyond lipophagy and include interaction with cytosolic lipolysis pathways, supply and expansion of lipid droplets, and lipoprotein trafficking.

FIGURE 1.

Overview of autophagic processes. Macroautophagy involves engulfment of cargo in a double membrane phagosome, which fuses with a lysosome to deliver contents for subsequent hydrolysis. In CMA, the adapter molecule HSC70 binds to the KFERQ motif in target proteins for translocation to the lysosome, where proteins enter directly through lysosome-associated membrane protein 2a for degradation. Microautophagy involves direct invagination of the lysosomal membrane for engulfment of cytosolic contents.

FIGURE 2.

Microlipophagy: ATG32 and ATG21 are required for formation of liquid-ordered microdomains, the site of lipid droplet internalization at the lysosome/vacuole surface. ATG14p and ATG6p localize to liquid-ordered microdomains and are involved in their expansion and lipid droplet internalization. The molecular machinery of lipophagy. Macrolipophagy: A variety of mechanisms recruit the autophagosome to the lipid droplet for engulfment and delivery to the lysosome. (Left) The GTPase Rab7 directly facilitates lipophagy and also recruits Rab10 to the lipid droplet. Rab10 forms a complex with EHBP1 and EHD2 to initiate lipophagy, potentially through membrane elongation along the LD surface. (Center) The lipid droplet surface protein PLIN2 can bind p62, a selective autophagy chaperone which binds LC3 on autophagosomes. (Right) AUP1 recruits the ubiquitin ligase Ube2g2 which ubiquitinates LD surface proteins. This ubiquitination may facilitate lipophagy through to-be-determined selective autophagy adapter binding to

autophagosomes. ATG, autophagy-related; LC3, light chain 3; PLIN2, perilipin 2; Ube2g2, ubiquitin conjugating enzyme E2 G2.

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FIGURE 3.

Regulation of lipophagy: (a) With high nutrient availability, mTOR is active and AMPK is inactive, resulting in reduced ULK1 activity and lack of autophagy/lipophagy initiation. mTOR also inactivates transcription factors including TFEB and TFE3 to prevent their transcriptional targeting of autophagy-lysosome genes. Lipophagy is also subject to transcriptional repression by FXR and epigenetic repression by LSD1. (b) In the fasted state, mTOR is inactive and AMPK is active, resulting in full ULK1 activity and initiation of autophagy/lipophagy. Further, transcriptional regulation of autophagy and lipophagy is fully engaged by a set of transcription factors including TFEB, TFE3, CREB, and FOXO. Beta adrenergic signaling induces lipophagy transcriptionally through activating PKA and CREB. AMPK, adenosine monophosphate-activated protein kinase; FOXO, forkhead box-O; FXR, farnesoid-X receptor; LSD1, lysine-specific histone demethylase 1; PKA, protein kinase A; TFEB, transcription factor EB.

FIGURE 4.

Alternative Roles for Autophagy in Lipid Metabolism (a) Chaperone-mediated autophagy targets PLIN2/3 for lysosomal degradation, allowing the machineries of lipophagy and cytosolic lipolysis to access lipid droplets. (b) Cytosolic lipases (ATGL/HSL) require binding to LC3 on the cytoplasmic face of autophagosomes for recruitment to the lipid droplet and activity. Autophagosomes also serve as scaffolds for MEK/ERK signaling activation of lipolysis. ATGL drives SIRT1-mediated induction of autophagy. (c) During starvation, autolysosomes deliver FFA to the ER for esterification and DGAT1-mediated TG synthesis to build lipid droplets. Subsequent cytosolic lipolysis at the LD fuels mitochondrial beta oxidation. (d). Autophagy clears aggregated and/or oxidatively modified ApoB, limiting secretion. Independently, Sortilin targets ApoB for autophagic degradation, limiting LDL formation and secretion. ApoB, apolipoprotein B; DGAT1, diacylglycerol O-acyltransferase 1; LC3, light chain 3; PLIN2, perilipin 2.