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Autophagy: nutrient and energy mobilization in need

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Abstract

Maintaining nutrient and energy homeostasis is crucial for the survival and function of cells and organisms in response to environmental stress. Cells have evolved a stress-induced catabolic pathway, named autophagy, to adapt to stress conditions such as starvation. During autophagy, damaged or non-essential cellular structures are broken down in lysosomes, and the resulting metabolites are reused for core biosynthetic processes or energy production. Recent studies have revealed that autophagy can target and degrade different types of nutrient storages and produce a variety of metabolites and fuels, including amino acids, nucleotides, lipids and carbohydrates. Here, we will focus on how autophagy functions to balance cellular nutrient and energy demand and supply, specifically, how energy deprivation switches on autophagic catabolism, how autophagy halts anabolism by degrading the protein synthesis machinery, and how bulk and selective autophagy-derived metabolites recycle and feed into a variety of bioenergetic and anabolic pathways during stress conditions. The recent new knowledge and progress in these areas provide a better understanding on resource mobilization and reallocation to sustain essential metabolic and anabolic activities under unfavorable conditions.

Introduction

In response to nutritional and energy crisis, cells need to make timely decisions to balance demand and supply, and to allocate limited resource to maintain viability and essential functions, at the expense of non-essential cellular structures and activities. Autophagy, derived from ancient Greek for “self-eating”, is a lysosomal catabolic pathway evolved for such function in eukaryotes from yeast cells to humans [1]. Compared to another cellular degradation pathway, the ubiquitin-proteasomal pathway, which degrades short-lived proteins and requires substrate proteins to be unfolded to feed into proteasomes, the substrates for autophagy are more versatile, including long-lived proteins, non-protein structures, or protein aggregates and organelles that are too large or unable to unfold for proteasomal degradation. Autophagy occurs at a low basal level under normal conditions, and its activity can be induced by a variety of stressors, such as starvation, ER stress, hypoxia, pathogen infection and exercise [1–3]. In response to nutrient deprivation, autophagy,

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but not the ubiquitin-proteasomal system, is the key mechanism to maintain energy production and cell survival [4].

The final destination of autophagy cargos is the lysosomal lumen wherein acid hydrolases degrade the delivered lysosomal contents to generate amino acids, fatty acids, nucleotides and sugars, which are recycled back to the cytoplasm and reused. Based on the mechanistic differences in cargo transportation and delivery to lysosomes, autophagy is categorized into three types: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). Macroautophagy (hereafter referred to as autophagy) involves the formation of classical double-membrane autophagosomes, which enwrap and transport cytosolic cargos to lysosomes for degradation. The nascent autophagosomal membrane is termed a phagophore. Autophagosomes are not present in microautophagy and CMA. Instead, microautophagy refers to the direct invagination of lysosomal membrane and subsequent degradation of incorporated cargos, which may resemble the formation of endosomal MVBs (multivesicular bodies) and require the ESCRT machinery (endosomal sorting complexes required for transport) [5]. CMA targets a specific subset of substrate proteins containing a KFERQ pentapeptide recognition motif, which are transported into lysosomes through the lysosome membrane receptor LAMP2A with the facilitation of a chaperone HSC70 [6]. All three autophagy pathways play important roles in regulating nutrient mobilization and energy homeostasis during stress times. A variety of key nutrients, including proteins, nucleic acids, carbohydrates and lipids, can be degraded by the three types of autophagy into the constituent amino acids, nucleotides, glucose and fatty acids for recycling and reuse. These catabolic pathways crosstalk with one another to provide building blocks for biosynthetic activities and feed into glycolysis and mitochondria for energy production (Figure 1). In this review, we will focus on the role and mechanism of autophagy-mediated mobilization of different types of nutrients under stress conditions (Table 1).

Autophagy activation: nutrient and energy sensing machinery

Execution of autophagy costs energy. Thus, the net energy gain from autophagy would be energy required for autophagosome formation subtracted from energy provided by autophagic cargo metabolism (Figure 2), although it is yet unclear how to quantitatively measure the energy expenditure and production during autophagy per time period. The energy needed to maintain the proton gradient and acidification in the lysosomal lumen is not considered in the formula due to the steady state of lysosomal existence. Induction of autophagy is orchestrated by more than 30 autophagy-related (ATG) genes, and originates from a variety of organelles that are in contact with the phagophore [7], including the ER (endoplasmic reticulum), mitochondria, recycling and late endosomes, the plasma membrane and lipid droplets (LDs), with ER subdomains and contact sites with other organelles proposed as the primary origin of autophagosomes thus far [8–11]. Autophagosome biogenesis is initiated by the serine-threonine protein kinase Atg1 (yeast)/ULK1 (mammalian, Unc-51 like autophagy activating kinase 1), which phosphorylates the regulatory subunits of the downstream pro-autophagic VPS34 PI3K (class III phosphatidylinositol 3-kinase) complex, including BECN1, ATG14 and AMBRA1 [12–16] (Figure 2). Phosphorylation of these subunits by ULK1 leads to activation of the lipid kinase VPS34 and production of phosphatidylinositol-3-phosphate (PI3P) at the phagophore. PI3P is a specific lipid

molecule of autophagosome vesicles, and recruits additional PI3P effectors (PI3P-binding autophagy proteins), including Atg18/WIPIs and their binding partner ATG2, to facilitate autophagosome expansion. ATG2 functions in membrane tethering, and also directly transfers phospholipids between membranes via an N-terminal hydrophobic pocket that can bind multiple glycerophospholipids [17–19]. Autophagosome membrane expansion also requires two ubiquitin-like conjugation systems, Atg8/LC3-PE (phosphatidylethanolamine) and the ATG12-ATG5-ATG16 complex. LC3 and ATG12 are the ubiquitin-like proteins in each system, and their conjugation requires a common E1-like enzyme, ATG7. Formation of the thioester linkage between the E1 ATG7 and its substrates (the ubiquitin-like proteins LC3 and ATG12) consumes energy (in the form of ATP hydrolysis). The subsequent E2-like enzyme for LC3 lipidation is ATG3, and for ATG12 conjugation is ATG10. The ATG12-ATG5-ATG16 complex promotes the lipidation of LC3 to PE and serves the role of an E3-like enzyme.

Subsequent incorporation of LC3-PE onto the forming autophagosome drives membrane expansion and cargo recruitment. During the last step of autophagy, autophagosomes fuse with lysosomes (or vacuoles in yeast) and form autolysosomes for substrate degradation. As other membrane fusion events in the cell, autophagosome-lysosome fusion requires the function of the SNARE (Soluble N-ethylmaleimide-sensitive factor Attachment protein REceptor) protein complex as a zipper to enclose two target membranes, which overcomes the high energy barrier of membrane fusion. STX17 (Syntaxin 17) is the autophagosomal membrane Q-SNARE, which provides a glutamine (Q) to the SNARE complex, and VAMP7 and VAMP8 are lysosomal membrane R-SNAREs that provide an arginine (R) to the SNARE complex. After digestion of autophagy substrates by lysosomal resident proteases, lipases and nucleotidases, a variety of lysosomal membrane nutrient transporters mediate the efflux of metabolites from the lysosomal lumen back to the cytosol, including amino acid transporters such as SLC38A9, LAAT-1 (also known as PQLC2), SNAT7 (also known as SLC38A7) and yeast Atg22, the sugar transporter SPIN, and ion channels such as MCOLN1 (also known as TRPML1) [20,21], some of which need the proton gradient for the efflux function [22]. These transporters play an important role in the maintenance of metabolite storage and nutrient balance in lysosomes.

The metabolic kinases mTORC1 (mammalian target of rapamycin complex 1) and AMPK (AMP-activated protein kinase) are two main upstream regulators of autophagy (Figure 2). mTORC1 is the central negative regulator of autophagy that phosphorylates ULK1 at S757 and suppresses ULK1 activity. mTORC1 also negatively regulates autophagy at the transcriptional level, by phosphorylating the master transcription factor of autophagy and lysosomal genes, TFEB (transcription factor EB), at multiple sites. Phosphorylation of TFEB promotes its nuclear export and shuts off autophagy gene transcription [23,24]. Activation of mTORC1 is mediated by small GTPases RagA/B, RagC/D, and Rheb, via a “coincidence detection” mechanism: mTORC1 is activated only when both growth factors (signals) and nutrients (building blocks) are present [21]. This is achieved by recruitment of mTORC1 to the lysosomal membrane by GTP-bound RagA/B and GDP-bound RagC/D (activated by cytosolic amino acid sensors and lysosomal cholesterol sensors), and activation of mTORC1 on the lysosomal membrane by GTP-bound Rheb (activated by growth factors). Therefore, deprivation of either growth factors or nutrients fails to activate mTORC1 and is

sufficient to switch on autophagy. In mice, although different organs show variable levels of autophagy capacity, autophagy is profoundly induced in most organs by 12–48 hours of nutrient deprivation, and only 2–4 hours of starvation in cell culture and single cell (such as yeast) systems [25–28]. AMPK plays a central role in metabolic regulation and is the major positive regulator of autophagy. AMPK is activated by low cellular energy (an increased AMP/ATP ratio) or low glucose availability (such as a low fructose-1,6-bisphosphate level) [29,30] (Figure 2). AMPK further phosphorylates autophagy proteins including ULK1 and BECN1 [31–33]. Different from mTORC1-mediated phosphorylation, phosphorylation of ULK1 by AMPK occurs at S555, which activates ULK1 and autophagy [33,34]. Together, deprivation of nutrients, growth factors, or energy robustly induces autophagy via inhibition of mTORC1 and/or activation of AMPK.

Regulation of bioenergetic balance by autophagy

Autophagy modulates both energy production and expenditure. Depletion of the autophagy protein ATG5 decreases hepatic β-oxidation induced by thyroid hormones [35], suggesting that autophagy positively regulates fatty acid β-oxidation in the liver. In brown adipose tissue, long-term cold stress also induces both autophagy and fatty acid β-oxidation [36], which is likely regulated centrally by anorexigenic POMC (proopiomelanocortin) neurons [37,38]. In theory, the best energy return of autophagy is for all autophagy-derived metabolites to be converted to acetyl-CoA and used as substrates in aerobic respiration by mitochondrial ATP synthase (Figure 1). Yet it is not the case in reality. Aside from contributing substrate metabolites to ATP production and biosynthetic pathways, cold stress-induced autophagy also enhances thermogenesis in brown adipose tissues [36]. Thermogenesis is a bioenergetic mechanism that homeotherms (warm-blooded animals), including birds and mammals, have evolved to maintain their body temperature and adapt to environmental changes, dissipating energy in the form of heat instead of ATP production. Thermogenesis is carried out by brown adipose tissues and beige adipose tissues that are rich in mitochondria, where protons flow into the mitochondrial matrix via Uncoupling protein 1 (UCP1), bypassing the ATP synthase. Accordingly, the three outcomes for autophagy-derived metabolites are: building blocks for biosynthetic pathways, ATP production, and thermogenesis (Figure 1).

The role of autophagy in controlling energy consumption is complex. Basal autophagy is required for white adipose tissue development [39–41] and autophagy activation promotes beige adipose tissue “whitening” by degrading mitochondria [42]. Inhibition of autophagy specifically in beige adipocytes by Atg5 or Atg12 KO is beneficial for beige fat maintenance and protects mice from high-fat diet (HFD)-induced obesity and insulin resistance [42]. In addition, although liver-specific inhibition of CMA causes hepatosteatosis after HFD feeding, such inhibition enhances, rather than decreases, hepatic energy expenditure and weight loss [43], which may be attributed to inhibited CMA degradation of metabolic enzymes, or compensatory upregulation of (macro)autophagy activity. Thus, on one hand, autophagy activation can remodel adipose tissue and liver, and render them less thermogenic with reduced energy expenditure; on the other hand, in response to cold stress autophagy enhances thermogenesis in mature brown adipose tissues [36], likely through improving mitochondrial quality control and providing metabolites and substrates. Future quantitative analyses are needed, preferentially in single cells or single populations of homogenous

cells, to model in what scenarios autophagy may contribute the highest ATP yield, in what scenarios autophagy may be energetically futile, and in what other scenarios autophagy balances energy demand and supply. In addition, the roles of autophagy in the regulation of resting energy expenditure (or basal metabolic rate) versus activity-induced energy expenditure are unclear and also require further investigation.

Other physiological conditions that dramatically increase energy demand, such as exercise, also activate autophagy. During intense exercise, the metabolic rate in contracting muscle can surge to nearly 100-fold [44], and rapid ATP production is essential to sustain exercise intensity and duration. Recent studies in both rodents and humans have demonstrated that aerobic exercise, as short as 30 min, potently activates autophagy in skeletal muscle [3,45–47]. A number of mechanisms have been proposed on how autophagy is activated in muscle during contraction, including energetic stress [48,49], oxidative stress [50], and transcriptional upregulation of autophagy genes by increased intracellular Ca^{2+} [51]. Prolonged endurance exercise results in net breakdown of muscle proteins (protein degradation rate > protein synthesis rate) and increased oxidation of amino acids, especially branched-chain amino acids (BCAAs), as energy source [52]. Such protein degradation even occurs during low-intensity exercise in McArdle's disease patients, who have defective glycogen phosphorylase and limited glycogen utilization as fuels in the muscle, evidenced by a high accumulation of non-metabolized amino acids, such as lysine, threonine and tyrosine that cannot be trans-aminated [53]. Thus, these findings suggest that exercise-induced autophagic breakdown is important to combat the negative energy balance during muscle contractions.

Protein catabolism to replenish amino acids, glucose and energy

Autophagy mediates both non-selective degradation of bulk proteins, and selective degradation of cargos via a receptor that binds both the autophagosome protein Atg8/LC3 and the cargo proteins (Figure 3, Table 1). Although an autophagosome in mammalian cells is small (0.5–2 μm in diameter) [54] and only occupies up to 0.1% of the cell volume, because the half-life of autophagosomes is short (<10 min), the degradative capacity of autophagy is high [55]. In the rat liver, the protein degradation rate is approximately 1.5% of total proteins per hour under normal conditions, compared to 4–5% of total proteins per hour under nutrient starvation conditions; the 3-fold increase in protein degradation is largely attributed to autophagy activation by starvation. In addition, organelle turnover is also mediated by autophagy. For example, mitochondria in hepatocytes have an average half-life of only 2–4 days [56,57], and are turned over by mitophagy (selective autophagic degradation of mitochondria).

Supplying amino acids and ATPs is an important function of autophagy for cells to survive starvation conditions. As discussed above, autophagy is induced when the cellular amino acid level drops to the threshold that is unable to activate mTORC1, or yeast mTOR homologs Tor1 and Tor2. Indeed, the initial screen for ATG genes was carried out in yeast for loss of viability in response to nitrogen starvation (cultured in a minimal synthetic medium without amino acids and nitrogen salt) [58]. Approximately half of autophagy-deficient Atg1-null yeast cells lose viability after cultured for 3 days in the nitrogen starvation medium, whereas wild-type (WT) cells maintain nearly 100% viability

after 5 days of cell culture. Furthermore, unlike WT cells, autophagy-deficient Atg7-null yeast cells are unable to restore intracellular amino acid levels after 3 hours of nitrogen starvation [59]. Autophagy-derived amino acids are used for protein biosynthesis, traced by ^{14}C-isotope labeled valine, especially for proteins crucial for yeast survival through amino acid starvation, such as Arg1 (argininosuccinate synthetase for arginine synthesis) and Hsp26 (heat shock protein of 26 kD with chaperone activity facilitating protein folding) [59]. In particular, autophagy-derived serine can be used to produce one-carbon (C1) unit molecules as starting materials for biosynthesizing various key anabolic precursors, which is essential for mitochondrial protein synthesis and metabolic remodeling for yeast to adapt from glycolytic to respiratory growth[60].

In mammals, autophagic degradation is important to maintain amino acid levels in newborns to survive the neonatal starvation period. Autophagy-deficient Atg5-null and Atg7-null mice are born at a normal Mendelian ratio, but die perinatally before milk suckling within one day after birth [61,62], which is partially rescued by force feeding. While not showing differences immediately after birth, the amino acid level in both the plasma and organs (such as heart, liver and brain), especially that of the essential amino acids and BCAAs, significantly drops in 10 hours. Consistently, Atg5-null embryos show early embryonic lethality at the 4–8-cell stage and decreased protein synthesis traced by ^{35}S-labelled methionine [63], suggesting that autophagy is essential for supplying amino acids as building blocks early in life (post-fertilization) during embryogenesis. In addition, AMPK is activated in Atg5-null, but not WT, newborns, suggesting that autophagy deficiency also causes energy deprivation. Notably, other nutrients, including blood glucose and fatty acid levels, are comparable between Atg5-null and Atg5-WT mice. These findings suggest that autophagy-provided amino acids, especially BCAAs, are used as an important energy source in newborns during the neonatal period. Oxidative degradation of BCAAs (such as leucine and isoleucine) generates acetyl-CoA, which can enter the TCA cycle and be oxidized for energy production. In addition to protein synthesis and ATP production, autophagy-produced amino acids are also used in glucose production in the liver via gluconeogenesis. Whole-body inducible or liver-specific Atg7 knockout (KO) adult mice are unable to maintain their blood levels of not only amino acids but also glucose during food deprivation [64,65]. Different from normal blood glucose levels in Atg-null newborns, these findings emphasize the importance of autophagy during adulthood in maintaining systemic glucose metabolism. Taken together, autophagy plays a key role in the maintenance of cellular and blood amino acid levels, housekeeping protein synthesis, energy production and survival during starvation.

Aside from synthesizing intracellular proteins, autophagy-derived amino acids can also be secreted, or contribute to the synthesis of secretory proteins. For example, alanine secreted through autophagic degradation in pancreatic stellate cells (myofibroblast cells that regulate extracellular matrix formation in the pancreas) can be utilized by neighboring pancreatic ductal adenocarcinoma (PDAC), which promotes tumor growth under nutrient-deprived conditions [66]. In addition, synthesis of secretory proteins, such as Interleukin-6/8, is dependent on the formation of a specialized location termed TASCC (TOR-autophagy spatial coupling compartment) under Ras-induced senescence conditions [67]. TASCC is a compartment where autolysosomes, mTORC1 and the secretory apparatus (including the rough ER and trans-Golgi network) are adjacent to one another, and thus is proposed

to spatially couple the catabolic and anabolic machineries for rapid protein turnover and resynthesis. Because TASCC forms under nutrient-rich conditions when both amino acids and growth factors are available, it is likely that mTORC1 is recruited to lysosomes by Rag and Rheb smOxidation and autophagy are critical energy providers duringall GTPases (Figure 2), but it is unknown what regulates the connection between the mTORC1-containing lysosomes and the secretory pathway.

Turnover of rRNAs and mRNAs to maintain nucleotide pool

In response to starvation, protein synthesis is halted. Under such conditions, autophagy mediates the degradation of the unnecessary protein translation machinery, including ribosomes and mRNAs [68–70]. Ribosomes constitute 30–40% of the cytosolic volume, and rRNA (ribosomal RNA) accounts for 80% of total cellular RNA [71], which can also serve as an abundant reservoir of amino acids and nucleotides. Autophagy-mediated selective degradation of ribosomes is termed as ribophagy, first identified in yeast and then in mammalian cells (Figure 4, Table 1). Ribophagy in both yeast and mammals is induced by starvation or Tor/mTORC1 inhibition, but the mechanisms in yeast versus mammalian cells are unclear and under debate. In yeast, ribophagy requires the core autophagy machinery and involves deubiquitination of ribosomal proteins by the ubiquitin protease Ubp3 and its cofactors Bre5, Cdc48 and Ufd3 [68,69] (Figure 4). Yet similar deubiquitination mechanisms have not been reported in mammalian cells. Instead, mammalian ribophagy is dependent on the PI3K components VPS34 and BECN1, but not ATG5 [72], resembling non-canonical autophagy that is ATG5-independent [73]. Notably, a receptor for ribophagy has recently been identified as NUFIP1 in mammalian cells [74] (Figure 4). NUFIP1 interacts with both ribosomes and the autophagosome protein LC3 to recruit ribosomes to forming autophagosomes, and is essential for ribosomal protein degradation and cell survival during starvation.

Autophagy mediates the degradation of RNAs, including rRNA and mRNA, to maintain cellular pools of nucleotides in response to starvation in yeast and higher eukaryotes. During starvation, Atg7 is essential for stabilizing the intracellular level of all four nucleosides (adenosine, guanosine, cytidine and uridine) in lung cancer cells [75]. Notably, nitrogen starvation induces a transient increase in nucleoside concentrations in yeast. Such increases peak at 1–2 hour after starvation and dependent on the core autophagy machinery, including Atg2 [76]. Although autophagy preferentially targets ribosome-bound translating mRNAs for vacuolar delivery [70], the ribophagy ubiquitin protease Ubp3-Bre5 is not required in this process [76], suggesting that autophagic degradation of RNAs is distinct from ribophagy and does not involve deubiquitination of ribosomes. Instead, in yeast, autophagic mRNA degradation requires the Atg24-Atg20 or the Atg24-Snx41 sorting nexin complexes. Via the autophagic regulation, mRNAs encoding proteins essential for anabolism, including ribosomal proteins and amino acid biosynthetic proteins, are degraded [70], which facilitates the shutdown of anabolic activities under stress conditions. Vacuolar/lysosomal RNA degradation is carried out by an evolutionarily conserved vacuolar T2 family acid ribonuclease, Rny1 in yeast and RNST-2 in C. elegans [70,76,77]. Loss of RNST-2 in C. elegans leads to lysosomal accumulation of rRNA, defects of embryonic and larval development, and a reduction in lifespan. Altogether, these findings highlight the dual

functions of autophagy in the switch-off of protein synthesis in response to starvation, and in the maintenance of nucleotide homeostasis during starvation and development.

Lipid mobilization by macro-, micro-, and chaperone-mediated autophagy

Starvation promotes a shift from carbohydrate metabolism to lipid metabolism for energy production, given glucose is scarce. Starvation induces hydrolysis of LDs to provide free fatty acids (FFAs) for oxidation and ATP generation. LDs are the intracellular lipid storage composed of neutral lipids, triglycerides (TGs) and cholesterol, surrounded by a phospholipid monolayer and coated by Perilipin coating proteins (PLINs). It is accepted that neutral lipids in the core of LDs are hydrolyzed by cytosolic lipases such as ATGL (adipose triglyceride lipase) (lipolysis) [78,79], whereas lysosomal lipases were thought to only degrade endocytosed lipoprotein-associated lipids. The discovery of macrolipophagy (macroautophagic degradation of lipids, hereinafter referred to as lipophagy) and visualization of LC3-labelled, LD-containing, double-membrane autophagosomes, initially in hepatocytes, largely expands our understanding on autophagy in nutrient mobilization [80] (Figure 5A, Table 1). Pharmacological or genetic inhibition of autophagy in vitro or in vivo leads to increased TG accumulation in diverse cell types, including hepatocytes, fibroblasts, vascular endothelial cells and neurons [80,81].

The function and destination of lipophagy-derived FFAs are still not fully understood. Cellular siRNA knockdown of Atg5, or hepatic-specific loss of Atg5 or Atg7, decreases lipid β-oxidation and ketone body production upon starvation [80,82], suggesting that lipophagy is essential for mitochondrial β-oxidation. However, additional evidences suggest that instead of being directly transported and utilized in mitochondria, lipophagy-derived FFAs are used to drive LD formation, or expression of β-oxidation enzymes via PPARα suppression [82,83]. Studies in mouse embryonic fibroblasts (MEFs) suggest that under starvation (amino acid- and growth factor-deprived) conditions, cytosolic lipases, rather than lipophagy, are required for the transport of FFAs from LDs to mitochondria [83]. By contrast, autophagy is essential for the growth of LDs in MEFs during starvation. Thus, it is plausible that in MEFs, instead of directly being transported to mitochondria for oxidation, lipophagy-derived FFAs are used for the formation of LDs; FFAs are then mobilized from LDs by cytosolic lipases and used in mitochondrial oxidation. Whether this FFA trafficking pathway also occurs in lipid-rich cells with higher lipid metabolism, such as hepatocytes or adipocytes, still awaits to be further investigated. In addition, fatty acids released by lipophagy in hypothalamic AgRP (agouti-related peptide) neurons are important for the expression of the orexigenic neuropeptide AgRP. Accordingly, specific KO of Atg7 in AgRP neurons leads to reduced body weight, fat mass, and food intake upon refeeding after starvation, although whether it impacts systemic glucose homeostasis or insulin sensitivity is yet unclear [81]. Another potential function of lipophagy-derived FFAs, other than mitochondrial oxidation, LD formation or gene expression, is to maintain circulating FFA levels and mediate cell-cell signaling, as lipophagy-derived FFAs have been reported to undergo efflux in hepatocytes via lysosomal fusion with the plasma membrane [84] (Figure 5A).

The molecular mechanism that governs LD recognition and degradation by lipophagy is poorly understood. LD size is suggested to be important for lipophagy targeting. In hepatocytes, only small LDs (with diameters less than 1 μm) are associated with the autophagosome protein LC3 and targeted for lipophagy, whereas large LDs are enriched with ATGL and broken down by cytosolic lipolysis [85], or undergo partial sequestration and then piecemeal degradation by lipophagy [80]. Given that ATGL is identified as a positive regulator of lipophagy [86], cytosolic lipolysis and lipophagy may synergistically and sequentially function to degrade LDs: ATGL-mediated cytosolic lipolysis occurs before lipophagy to produce smaller LDs to fit in the size of autophagosomes. In the brown adipose tissue and liver, cold stress activates autophagy and promotes the association of LDs with several autophagy proteins, including ATG12-ATG5, BECN1 and LC3 [38], suggesting that these proteins may function in autophagosomal incorporation of LDs. Although another autophagy protein ATG2 is also found to localize on the LD surface and Atg2 knockdown causes LD enlargement in mammalian cells, such LD accumulation is not dependent on other components of the autophagy machinery, such as ATG5 [87]. Given the lipid transferring ability of ATG2 [17–19], it is reasonable to speculate that ATG2 may mobilize the phospholipids at the surface of LDs and increase the accessibility for breakdown. After LDs are delivered in autolysosomes, Dyn2 (Dynamin 2), a GTPase functioning in membrane scission and separation, is found to associate with the autolysosomal tubules and promote lysosomal fission and reformation [88]. Inhibition of Dyn2 causes elongated autolysosomal structures, ultimate lysosome depletion and impaired LD breakdown under nutrient-deprived conditions in hepatocytes, and is associated with ethanol-induced liver steatosis [88,89]. It remains to be determined whether Dyn2-mediated lysosome reformation is also universally important for (auto)lysosomal degradation of diverse substrates.

Two other types of autophagy, CMA and microautophagy, also contribute to lysosome-mediated LD degradation. The LD coating protein PLIN2 contains a KFERQ-like CMA-targeting motif, and is phosphorylated in an AMPK-dependent manner [90] and degraded by CMA during starvation [91] (Figure 5B, Table 1). Mutating the CMA-targeting motif in PLIN2 blocks its degradation by CMA, and leads to accumulation of LDs and inhibition of both cytosolic lipolysis and lipophagy. Thus, CMA plays a key role in providing access of the lipid core to both cytosolic lipases and the autophagy machinery. In addition, the use of CMA-deficient cells may also shed light on the mechanism of lipophagy, as these cells show reduced recruitment of a number of autophagy proteins to LDs, including BECN1, ATG5, LC3 and NBR1 (another autophagy cargo receptor), suggesting that these autophagy proteins may participate in the initiation of lipophagy.

Furthermore, in both yeast and mammalian cells, micro-lipophagy (μ-lipophagy), the selective degradation of LDs by microautophagy, also contributes to lipid utilization and survival in response to lipid stress and nutrient deprivation (Figure 5C, Table 1). In yeast, during adaptation to ER stress or lipid imbalance, for example, defective PC (phosphatidylcholine) biosynthesis, caused by KO of the key enzyme Cho2 (*cho2*Δ cells), promotes LD formation at the ER to convert phospholipids to TGs as a storage. These LDs are degraded via direct engulfment by the vacuole, representing micro-lipophagy [92,93]. Similar to microautophagy, micro-lipophagy does not require the core ATG proteins such as Atg7, but requires the ESCRT complex and an ER membrane protein Atg39 (Autophagy-

related protein 39, locus: Ylr312c, also identified as a receptor for reticulophagy and nucleophagy, the selective autophagic degradation of the ER and nucleus). It is likely that Atg39 is a multi-functional receptor in different autophagic pathways targeting various ER-associated structures or domains, including the LDs and nucleus. Yeast micro-lipophagy is also induced by acute glucose restriction via AMPK activation [94]. At the vacuolar membrane surface, the PI3K components Atg14 and Atg6 (BECN1 homolog) are enriched at liquid-ordered domains (specific membrane regions with fast diffusion and high-acyl-chain order) to facilitate LD recruitment and membrane invagination. In mammalian hepatocytes, direct contact and piecemeal lipid transfer between LDs (and the LD protein PLIN2) and lysosomes are observed, which morphologically resemble micro-lipophagy [95]. Neither the core autophagy protein ATG5, nor the CMA receptor LAMP2A, is required for lipid delivery to lysosomes under such conditions, genetically supporting that it is micro-lipophagy in mammalian systems. The genetic regulators of mammalian micro-lipophagy remain to be discovered, but the ESCRT complex and homologs of the aforementioned yeast autophagy proteins, including BECN1 and ATG14, may serve as candidates for investigation. Altogether, all three autophagy pathways are utilized as an important survival strategy that drives LD turnover and lipid mobilization upon stress.

Regulation of glucose homeostasis by glycophagy

Autophagy plays an important role in glucose metabolism via autophagic degradation of glycogen (glycophagy) [96,97] (Figure 6, Table 1). Glycogen is a polysaccharide of glucose and a main source of intracellular glucose storage in the liver. Similar to LDs, glycogen can be degraded in both the cytosol and the lysosome. In the cytosol, glycogen is broken down via glycogenolysis, the sequential release of glucose-1-phosphate by the cytosolic enzyme, glycogen phosphorylase [98]. Cytosolic glucose-1-phosphate is then be isomerized by phosphoglucomutases into glucose 6-phosphate, which can be used intracellularly, or further transported into the ER via the glucose 6-phosphate transporter (G6PT). Inside the ER, glucose 6-phosphate is dephosphorylated by glucose 6-phosphatase to produce free glucose that can be released extracellularly via glucose transporters as fuel for other organs. In comparison, lysosomal glycogen degradation generates non-phosphorylated free glucose that can be readily released. In glycophagy, glycogen is delivered to lysosomes by autophagosomes, and then hydrolyzed into single α-glucose molecules by lysosomal acid α-glucosidase (GAA). Besides liver, muscle also stores glycogen as its energy source. Genetic deficiency in GAA leads to myopathies such as glycogen storage disease type II (also known as Pompe disease), manifested by glycogen accumulation in lysosomes [99].

Glycophagy and cytosolic glycogenolysis can complement each other in glucose production. Glucose released from glycophagy can be further used in the synthesis of fatty acids, nucleotides and nucleic acids, and aromatic amino acids. It should be noted that under normal conditions, lysosomes are responsible for degrading only 1–3% of cellular glycogen, and more glycogen may be degraded by cytosolic glycogenolysis. Because of this reason, energy deprivation or low blood glucose levels are not observed in Pompe patients. However, under stress conditions when the glucose demand increases, glycophagy may play a more important role in glycogen degradation. Indeed, upon 24-hour starvation, glycophagy can almost completely compensate for glycogenolysis in the muscle of drosophila larva

[100]. In comparison with glucose release from glycogenolysis, which requires coordinated activities of many enzymes and transporters for (de)phosphorylation and trafficking, glycophagy directly produces free glucose and may be a more efficient mechanism to supply glucose to the circulation under stress conditions.

Glycophagosomes (glycogen-containing autophagosomes) are observed in drosophila and mice during development [100,101]. In mice, glycophagosomes are found within glycogen granules during mouse embryogenesis in brown adipose tissue, where glycogen breakdown is essential for LD formation. However, because genetic inhibition studies or screens on the autophagy machinery (ATG genes) in glycogen degradation are lacking, the molecular mechanism of glycophagy is still poorly understood. Of note, skeletal muscle-specific KO of Atg5 in GAA KO mice, a Pompe disease mouse model, does not ameliorate lysosomal glycogen accumulation in the muscle [102], suggesting that similar to ribophagy (discussed above), glycophagosome formation and glycophagy may be carried out by the ATG5-independent non-canonical autophagy mechanism [73]. Nevertheless, starch binding domain-containing protein 1 (STBD1) has been identified as a receptor for glycophagy in mammalian cells (Figure 6). STBD1 is associated with glycogen and interacts with the Atg8/LC3 family members GABARAP and GABARAPL1, presumably via an LC3-interacting region (LIR) motif [103,104]. Yet intriguingly, STBD1 appears to be a liver-specific receptor, because depleting Stbp1 in GAA KO mice reduces lysosomal accumulation of glycogen only in the liver, but not skeletal muscle or heart [105,106]. Therefore, it is possible that either glycophagy in muscle tissues is non-selective and does not require a receptor, or there are muscle-specific receptors that mediate glycogen transport and glycophagy in muscle, which are worthy of further investigation as potential therapeutic targets against Pompe disease.

Concluding remarks and unanswered questions

Although autophagy has been shown to play an important role in intracellular nutrient mobilization and re-utilization, there are many unanswered questions. The molecular mechanisms, especially at the cargo recognition and delivery step, of selective autophagic degradation of different nutrient storages, including lipophagy and glycophagy, are not fully understood. There is also a lack of quantitative knowledge on the capacity of autophagy-mediated nutrient storage degradation under stress conditions (compared to cytosolic nutrient breakdown pathways, for example, lipolysis versus lipophagy, and glycogenolysis versus glycophagy), and on the effect of pharmacological autophagy inducers and inhibitors on nutrient mobilization and flow. Besides starvation, how autophagy mediates nutrient mobilization in response to additional stressors, such as exercise and cold stress, is largely unknown and needs further characterization. Furthermore, in addition to direct intracellular nutrient catabolism, the autophagy machinery may carry out a secretory function in higher eukaryotes. Many autophagy proteins have recently been shown to regulate the secretion of a variety of hormones, cytokines and neurotransmitters [107–111]. Further understanding of the non-autophagic roles of ATG proteins may shed light on the noncell autonomous intercellular communication in systemic energetics of multicellular organisms. Lastly, the roles of autophagy in different tissues, genders and/or ages in mammalian nutrient mobilization are understudied. For example, in Pompe disease, why liver is not as sensitive

as muscle to glycophagy defects is unclear. It is worthy of further study on how diverse tissues adapt to their different metabolic activity and energy demand under healthy and pathological conditions.

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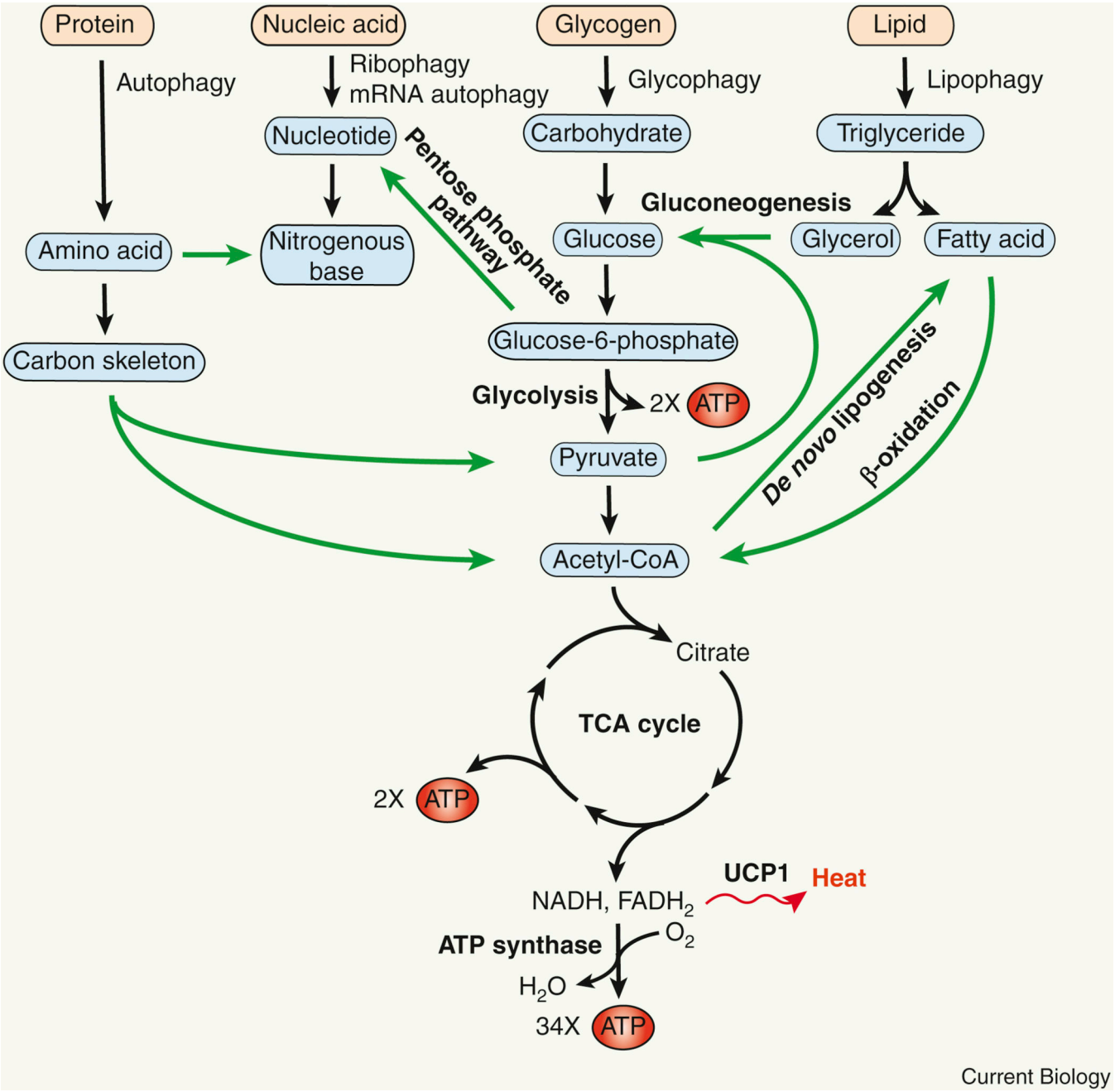

Figure 1. Schematic illustration of autophagic metabolism of proteins, nucleic acids, carbohydrates and lipids, and their crosstalk in energy production.

The amount of energy produced per glucose molecule (or equivalent precusors) is: 2 ATPs from glycolysis, 2 ATPs from the tricarboxylic acid (TCA) cycle, and a maximum of 34 ATPs by the ATP synthase of the mitochondrial electron transport chain. Autophagy-generated energy is also dissipated as heat via mitochondrial UCP1 (Uncoupling protein 1). Communication among different nutrient metabolic pathways is highlighted by green arrows.

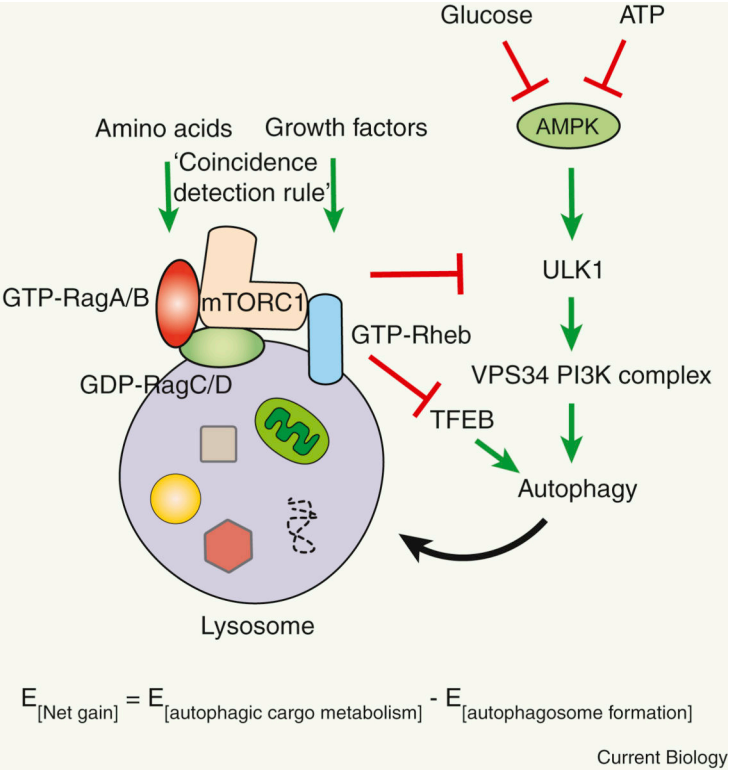

Figure 2. mTORC1-mediated inhibition and AMPK-mediated activation of autophagy via nutrient-, growth factor-, and energy-sensing.

Amino acids activate Rag GTPases, and growth factors activate the Rheb GTPase. Active Rag GTPases (GTP-bound RagA/B and GDP-bound RagC/D) and the active Rheb GTPase (GTP-bound Rheb) synergistically recruit and activate mTORC1 on the lysosomal membrane. Active mTORC1 phosphorylates and inhibits the autophagy-initiating kinase ULK1 and the master transcriptional regulator of autophagy TFEB. By contrast, AMPK senses low glucose and ATP levels, and activates ULK1 and the downstream VPS34 PI3K complex to activate autophagy. Autophagy delivers a variety of substrates, including proteins, organelles (such as ribosomes and associated RNAs), lipid droplets (LDs), glycogen and iron storages, to the lysosome for degradation, which promotes nutrient mobilization for biosynthesis and energy production in response to nutrient and energy depletion. E, energy.

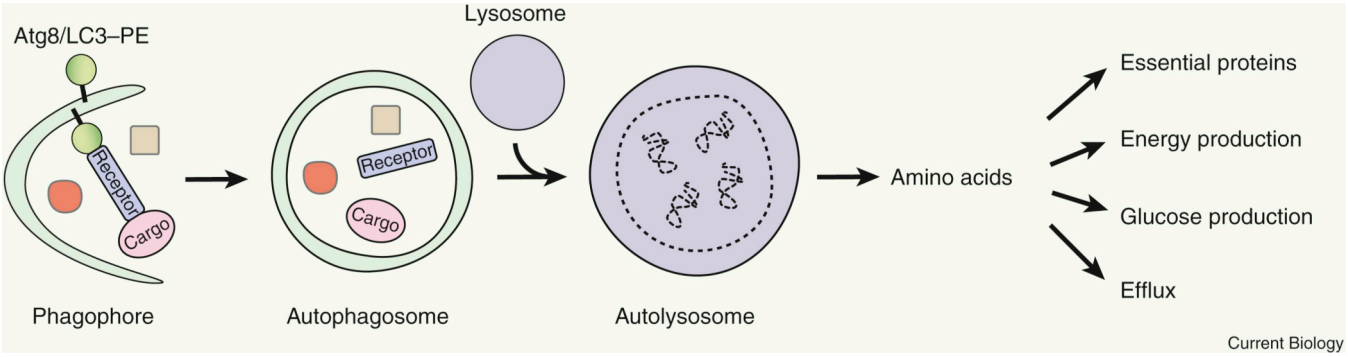

Figure 3.

Amino acids produced by non-selective bulk autophagy, or selective autophagy via a receptor that binds both Atg8/LC3 and the cargo, fulfill diverse functions of the cell.

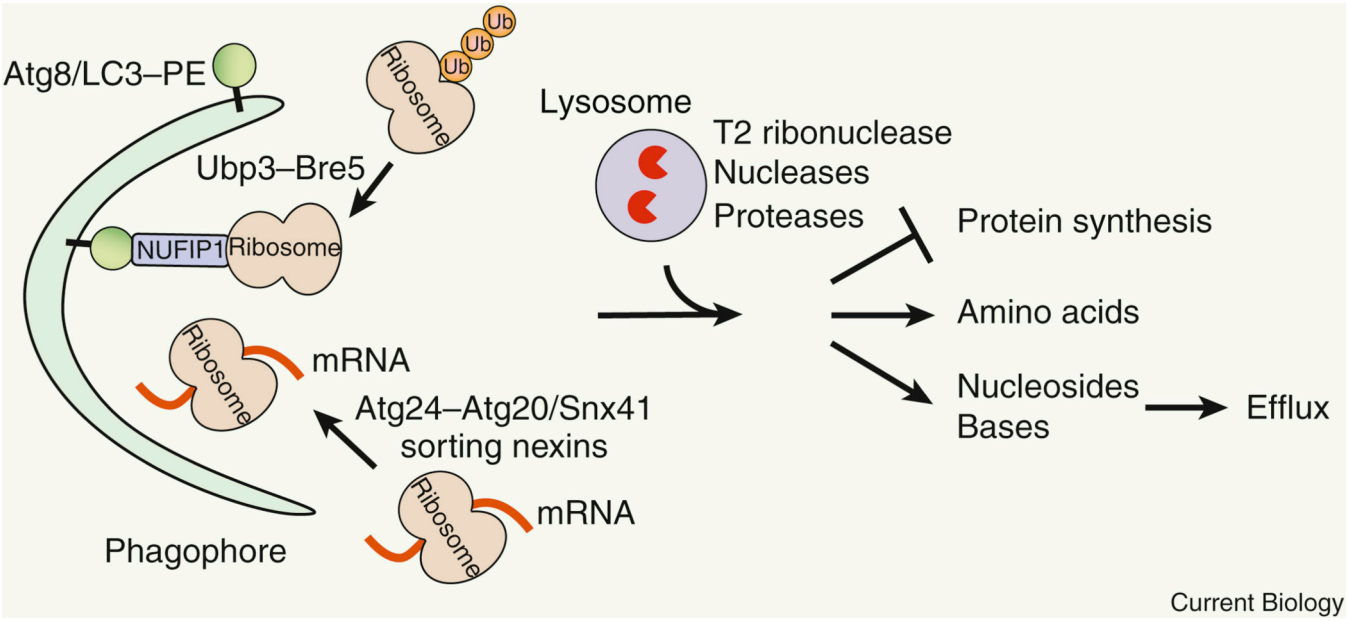

Figure 4. Degradation of ribosomal proteins, rRNA and ribosome-bound translating mRNA by ribophagy or autophagy-mediated RNA degradation.

Ribophagy and mRNA autophagy switches off protein synthesis and provides amino acids, nucleosides and bases, which can be further secreted outside of the cells. In yeast, deubiquitination of ribosomal proteins by the Ubp3-Bre5 ubiquitin protease is required for ribophagy. In mammalian cells, NUFIP1 serves as a ribophagy receptor that binds both LC3 and ribosomes. Autophagic sequestration of mRNAs requires Atg24-Atg20 or Atg24-Snx41 sorting nexin complexes in yeast. Ub, ubiquitin.

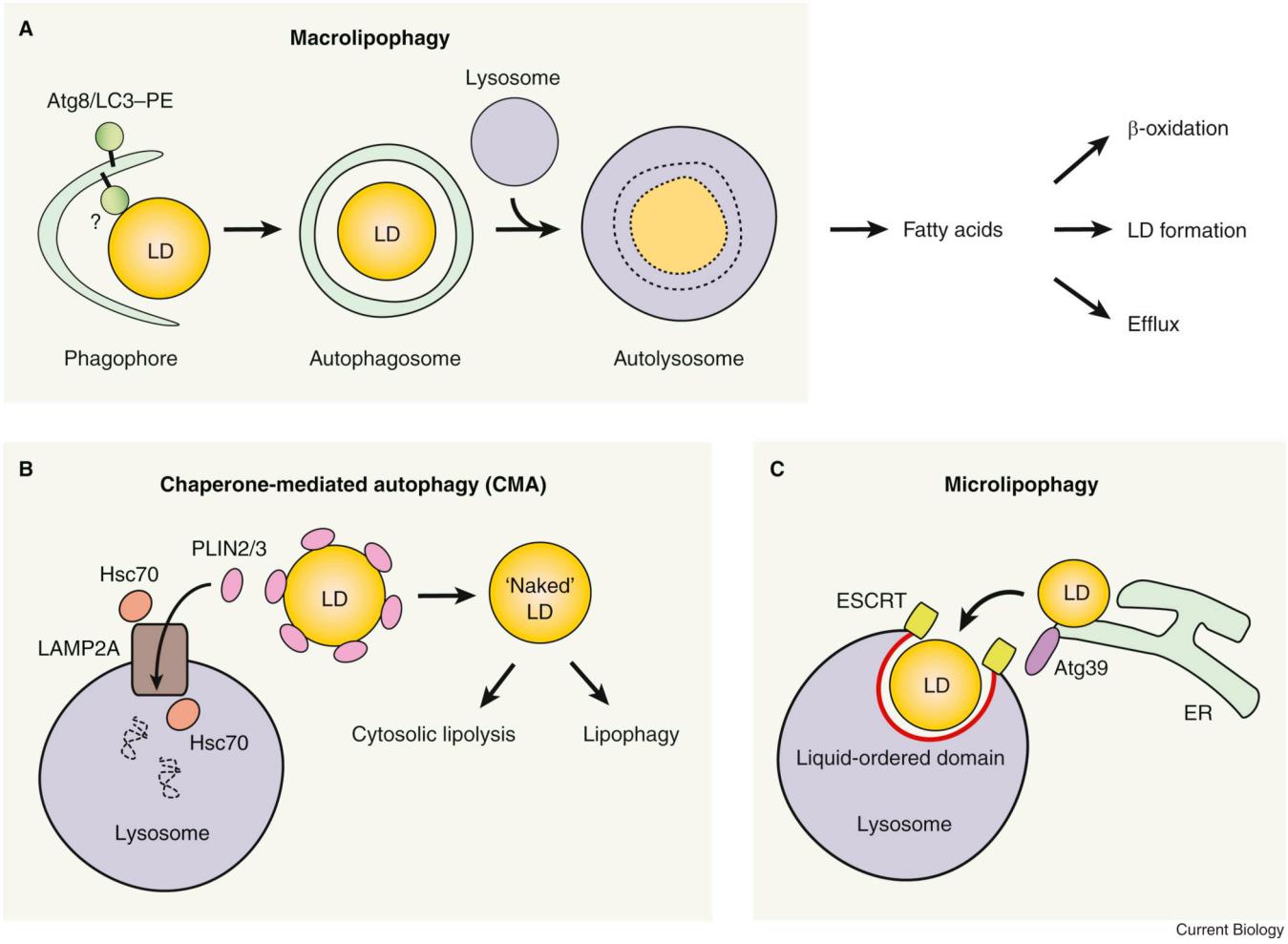

Figure 5. Lipid mobilization by three types of autophagy.

(A) Fatty acids are produced by macrolipophagy (lipophagy) of LDs. It is unclear whether a receptor protein is required in macrolipophagy. **(B)** Chaperone-mediated autophagy degrades LD coating proteins PLIN2 and PLIN3, and increases the accessibility of the "naked" LDs to both cytosolic lipolysis and lipophagy. **(C)** Micro-lipophagy mediates the direct engulfment of LDs by the vacuole/lysosome at the liquid-ordered domain. ESCRT proteins, Atg39 and a number of autophagy proteins are involved in micro-lipophagy.

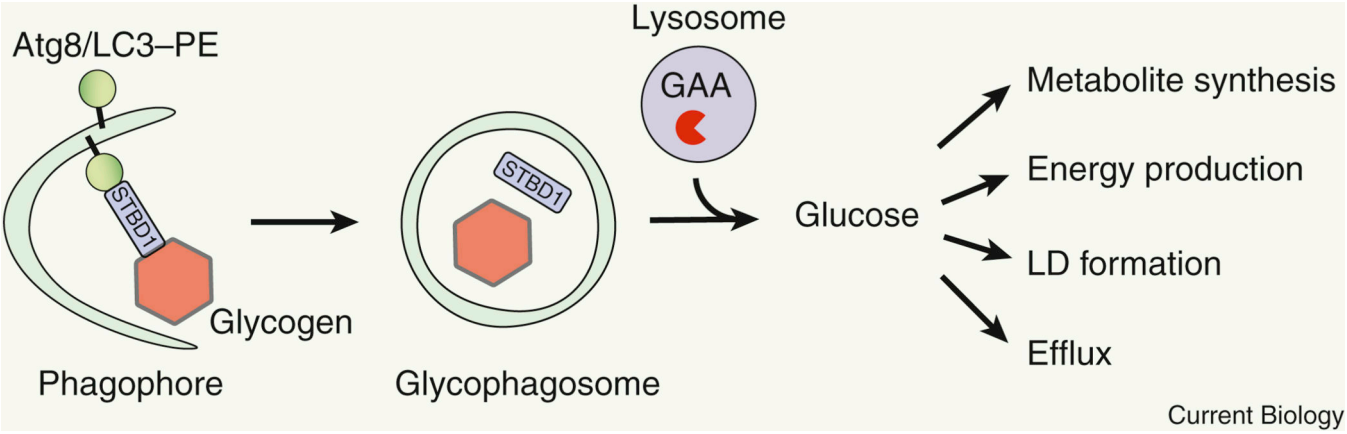

Figure 6. Selective autophagic degradation of glycogen.

Glycogen is degraded in lysosomes by glycophagy via a receptor STBD1. Glucose is released for many anabolic functions. GAA, lysosomal acid α-glucosidase. LD, lipid droplet.

Table 1.

Regulatory machinery and physiological outcomes of abnormal autophagy-regulated nutrient mobilization.

Type of recycled nutrient	Regulatory machinery	Organism/tissue	Disease-relevant phenotypes if defective	References
Energy production and consumption	Atg5	Mouse/brown adipocyte, liver	Reduced β-oxidation and thermogenesis	36,35
	Atg7	Mouse/POMC neuron	Reduced energy expenditure, hyperglycemia	37,38
	Atg5, Atg7, Atg12	Mouse/white and beige adipocytes	Adipocyte “browning”, lean body mass, improved glucose tolerance and insulin sensitivity	39–41,42
	LAMP2A-mediated CMA	Mouse/liver	HFD-induced hepatosteatosis, lean body mass, enhanced energy expenditure	43
Protein → amino acids	Atg1, Atg7	Yeast	Unable to restore intracellular amino acid levels and survive during starvation	58,59
	Atg5, Atg7	Mouse/whole body	Neonatal lethality, energy deprivation	61,62
	Atg7	Mouse/liver	Low circulating amino acids and glucose	64,65
	Atg5, Atg7	Pancreatic stellate cell	Reduced growth of pancreatic ductal adenocarcinoma	66
Ribophagy → amino acid + nucleotide	The ubiquitin protease complex Ubp3-Bre5-Cdc48-Ufd3	Yeast	Uncontrolled ribosome abundance	68,69
	NUFIP1, VPS34, BECN1, ATG7	Mammalian cells	Reduced cellular nucleotide pools and cell survival during starvation	72,74,75
mRNA autophagy → nucleotide nucleotide nucleotide	Atg2, Sorting nexin Atg24-Atg20 and Atg24-Snx41	Yeast	Elevation of mRNAs encoding amino acid biosynthesis and ribosomal proteins	70,76
	T2 ribonuclease RNST-2	C. elegans	Defective embryonic and larval development, reduced lifespan	73
Lipid → fatty acid	Atg5, Atg7	Mammal cells	Increased TG accumulation	80,81
	Atg7	Mouse/AgRP neuron	Reduced food intake and lean phenotype	81
	LAMP2A-mediated CMA	Mammalian cells	LD accumulation	91
	Atg39 and ESCRT- mediated microlipophagy	Yeast, hepatocyte	LD accumulation upon ER stress, defects in mitochondria and ER morphology and cell growth upon lipid stress	92,93,95
Glycogen→glucose	GAA	Mouse/muscle and brown adipose tissue, drosophila	Pompe disease	100–102
	STBD1	Mouse/liver	Ameliorated lysosomal glycogen storage	105,106