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CELL DEATH AND AUTOPHAGY

Autophagy at the crossroads of catabolism and anabolism

Jasvinder Kaur and Jayanta Debnath

Abstract | Autophagy is a conserved catabolic process that degrades cytoplasmic constituents and organelles in the lysosome. Starvation-induced protein degradation is a salient feature of autophagy but recent progress has illuminated how autophagy, during both starvation and nutrient-replete conditions, can mobilize diverse cellular energy and nutrient stores such as lipids, carbohydrates and iron. Processes such as lipophagy, glycophagy and ferritinophagy enable cells to salvage key metabolites to sustain and facilitate core anabolic functions. Here, we discuss the established and emerging roles of autophagy in fuelling biosynthetic capacity and in promoting metabolic and nutrient homeostasis.

Ubiquitin–proteasome system
(UPS). The cellular quality control pathway that tags and degrades unwanted or superfluous proteins.

Basal autophagy
A constitutive autophagic degradation process that proceeds in the absence of any overt stress or stimulus and serves important housekeeping roles.

Autophagosomes
Double membrane-bound vesicles that sequester cytoplasmic materials and target them for lysosomal degradation during macroautophagy.

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Autophagy, the process of cellular self-eating, has long been recognized as an important protein degradation pathway, particularly during starvation or stress. In contrast to the ubiquitin–proteasome system (UPS), which targets individual short-lived proteins, autophagy functions as a bulk process with the capacity to degrade long-lived proteins and organelles such as the endoplasmic reticulum, mitochondria, peroxisomes, the nucleus and ribosomes[1,2]. Evidence indicates that autophagic degradation promotes the recycling and salvage of cellular nutrients, thereby enabling cell survival during starvation. Autophagy, along with the UPS, is also a key mechanism for protein homeostasis and quality control. Indeed, basal autophagy within cells is important for the degradation of damaged and dysfunctional proteins and organelles; autophagy-deficient mice exhibit a build-up of misfolded, damaged proteins[3–5] (BOX 1).

Although protein degradation is a salient feature of autophagy, studies over the past decade have revealed that autophagy plays a key part in mobilizing diverse cellular energy and nutrient stores, including carbohydrates, lipids and minerals. Hence, a growing appreciation of the role of autophagy in controlling cellular metabolism in both normal and diseased cells has fuelled immense interest in elucidating how dysfunctional autophagy influences metabolic disorders and metabolic adaptation in diseases such as cancer. Here, we provide a brief overview of the autophagic process before reviewing the established and emerging roles of the catabolism of proteins, lipids (lipophagy), carbohydrates (glycophagy) and iron (ferritinophagy) in fuelling energy and nutrient stores. We also delineate how autophagy facilitates the adaptive metabolic response and supports anabolic pathways within cells.

Overview of the autophagic pathway

Autophagy refers to a collection of tightly regulated catabolic processes, all of which deliver cytoplasmic components to the lysosome for degradation, and that are broadly classified into three types: macroautophagy, microautophagy and chaperone-mediated autophagy (FIG. 1a). Macroautophagy involves the formation of double membrane-bound vesicles called autophagosomes that engulf cytoplasmic proteins and organelles; these autophagosomes are trafficked to lysosomes, at which point the sequestered cargo is degraded[6]. Microautophagy refers to the invagination of the lysosomal or endosomal membrane, resulting in the direct engulfment of substrates that are subsequently degraded by lysosomal proteases[7]. Chaperone-mediated autophagy is distinct from macroautophagy and microautophagy because cargo is not sequestered within a membrane delimited vesicle. Instead, proteins targeted by chaperone-mediated autophagy contain a KFERQ-like pentapetide motif that is recognized by the cytosolic chaperone heat shock cognate 70 kDa protein (HSC70); HSC70 promotes the translocation of these targets across lysosomal membranes into the lysosomal lumen via the lysosomal-associated membrane protein 2A (LAMP2A) receptor[8]. This Review focuses on macroautophagy, which we hereafter call autophagy. Although the molecular regulation of autophagy remains an active area of research, immense progress over the past decade has been made in two areas: our understanding of the biogenesis of the autophagosomal membrane and of the molecular control of selectivity. This section provides a brief overview of these two topics; more detailed reviews on the molecular regulation of autophagy are found elsewhere[2,9,10].

Box 1 | **Autophagy and protein quality control**

In addition to its importance in protein catabolism during starvation, basal autophagy is now recognized as a critical housekeeping pathway even in nutrient-rich conditions. This quality control mechanism is particularly crucial in postmitotic tissues, such as nerve and muscle, where autophagy is important for the removal of aggregated proteins and, therefore, for protecting the cells from the toxic effects of dysfunctional proteins that cannot be diluted via cell division[113]. Loss of autophagy in neurons or cardiac muscles can result in the accumulation of ubiquitylated proteins and inclusion bodies, leading to neurodegeneration and cardiac hypertrophy, respectively[114,115]. Constitutive autophagy in non-stressed conditions is therefore critical for the turnover of intracellular proteins and for maintaining cell homeostasis.

In serving these functions, autophagy cooperates with another key protein degradation pathway, the ubiquitin–proteasome system. Robust activation of autophagy has been observed upon the pharmacological inhibition of the proteasome or the genetic ablation of proteasome components[116,117]. In these situations, autophagy is proposed to remove oligomeric protein aggregates that are potentially deleterious to cells. Autophagy is also important for the replenishment of intracellular amino acid pools in response to proteasome inhibition[118], which is consistent with findings showing that proteasomes are critical for protein synthesis as they maintain amino acid levels[119]. Alternatively, proteasome activation can suppress autophagy by increasing amino acid levels and constitutively activating mammalian TOR complex 1 (mTORC1)[120].

Finally, autophagy has a pro-survival role during endoplasmic reticulum (ER) stress as it acts as an alternative mechanism for the clearance of misfolded or damaged proteins that cannot be cleared by the unfolded protein response. Autophagy selectively degrades aggregated proteins that accumulate in the ER lumen, such as the mutant secretory protein α1-antitrypsin[121]. Additionally, studies of yeast and mammalian cells demonstrate that autophagy mediates ER homeostasis by selectively segregating portions of this organelle network; this process has been termed ER-phagy or reticulophagy[122–125].

Autophagosome biogenesis. The earliest step of autophagy is characterized ultrastructurally by the sequestration of portions of cytoplasm into a double membrane-bound vesicle called the autophagosome. The autophagosome subsequently fuses with a lysosome, leading to the degradation of the sequestered cytosolic proteins and organelles[9]. Studies in yeast have identified more than 30 autophagy-related proteins (ATGs), many of which have identified mammalian orthologues[11,12]. As depicted in FIG. 1a, autophagosome formation comprises three main steps: initiation, nucleation and expansion of the isolation membrane. The intricate process of autophagosome formation begins at the phagophore assembly site (also known as the isolation membrane) where proteins of the UNC51-like kinase (ULK) complex (which is composed of ULK1 or ULK2 and ATG13, FAK family kinase interacting protein of 200 kDa (FIP200) and ATG101) assemble to initiate autophagosome formation[9]. Next, in the nucleation stage, the activated ULK complex targets a class III PI3K complex — consisting of beclin 1 (Atg6 in yeast), vacuolar protein sorting 15 (VPS15), VPS34 and ATG14 — to promote the local production of a pool of phosphatidylinositol 3-phosphate that is specific to autophagosomes. Interestingly, a recent study revealed that ATG14 also promotes the fusion of autophagosomes with the endolysosomal compartment[13]. Finally, in the expansion stage, the ATG12–ATG5–ATG16 complex is recruited to the autophagosome membrane where it facilitates the lipidation of microtubule-associated protein 1 light chain 3 (MAP1LC3; also known as LC3) with phosphatidylethanolamine; LC3 is the chief mammalian homologue of yeast Atg8, which is required for the expansion of the isolation membrane. Recent research indicates that the deacetylation and cytosolic translocation of a nuclear pool of LC3 is required for its lipidation with phosphatidylethanolamine during starvation-induced autophagy[14].

In contrast to yeast, in which the initial phagophore assembly site is likely to be assembled *de novo*[15,16], the origin of membranes contributing to autophagosome formation in mammalian cells has been intensely debated and scrutinized. Although evidence supports the idea that nucleation of the isolation membrane occurs at a distinct site emanating from the endoplasmic reticulum (ER), termed the omegasome[17], other sources of membrane contribute to autophagosome formation, including ER–Golgi intermediate compartments, ER–mitochondria junctions, mitochondria, endosomes and the plasma membrane[17–22]. Taken together, these studies highlight the complexities of autophagy initiation in mammals. Given the diversity of stimuli and stresses that can induce autophagy, an important area of future research is determining whether and how these varied membrane sources are utilized for autophagy in response to specific stimuli.

Selective autophagy. Nutrient starvation-induced autophagy was originally believed to non-selectively sequester and degrade cytoplasmic material. However, it is increasingly being appreciated that autophagy is a selective process, resulting in the targeted engulfment of specific cargoes such as mitochondria, peroxisomes and ribosomes, and protein aggregates. Selective autophagy is mediated by autophagy cargo receptors that bind cargo earmarked with degradation signals, most commonly ubiquitin in mammals, through their ubiquitin-binding domain (UBD). These receptors also commonly possess a motif called the LC3 interacting region (LIR), which mediates their binding to Atg8 (LC3 in mammals) isoforms present on newly developing autophagosomes (FIG. 1b). As a result, autophagy cargo receptors act as molecular bridges that capture ubiquitylated proteins targeted for degradation by the autophagy pathway and complement the UPS. For example, the autophagy cargo receptors p62 (also known as SQSTM1), NBR1 (next to *BRCA1* gene 1 protein) and histone deacetylase 6 (HDAC6) all promote the autophagic clearance of protein aggregates in a process known as aggrephagy, which is dependent on both the UBD and LIR[2,10]. In yeast, although orthologues of UBD-containing adaptor proteins such as p62 are missing, a recent mass spectrometric study identified Cue5 as a potential autophagy cargo receptor[23]. Cue5 possesses a coupling of ubiquitin-conjugation to ER degradation (CUE) domain, which is structurally related to mammalian UBDs and is capable of binding to ubiquitin as well as interacting with Atg8. Hence, Cue5 is a ubiquitin–Atg8 adaptor protein that functions analogously to p62 in mammals to mediate the selective autophagic degradation of ubiquitylated targets. Both yeast Cue5 and its mammalian orthologue, Toll interacting protein (TOLLIP), target aggregation-prone proteins that cannot be cleared by the UPS, such as huntingtin, for autophagic degradation[23].

Unfolded protein response
The activation of a stress response in the endoplasmic reticulum due to an increase in misfolded or aggregated proteins.

Autophagy-related proteins
(ATGs). Autophagy regulators.

Autophagy cargo receptors
Adaptor proteins that mediate the targeting of autophagosomes to cargo (for example, mitochondria and protein aggregates), often via ubiquitin and LC3-binding domains.

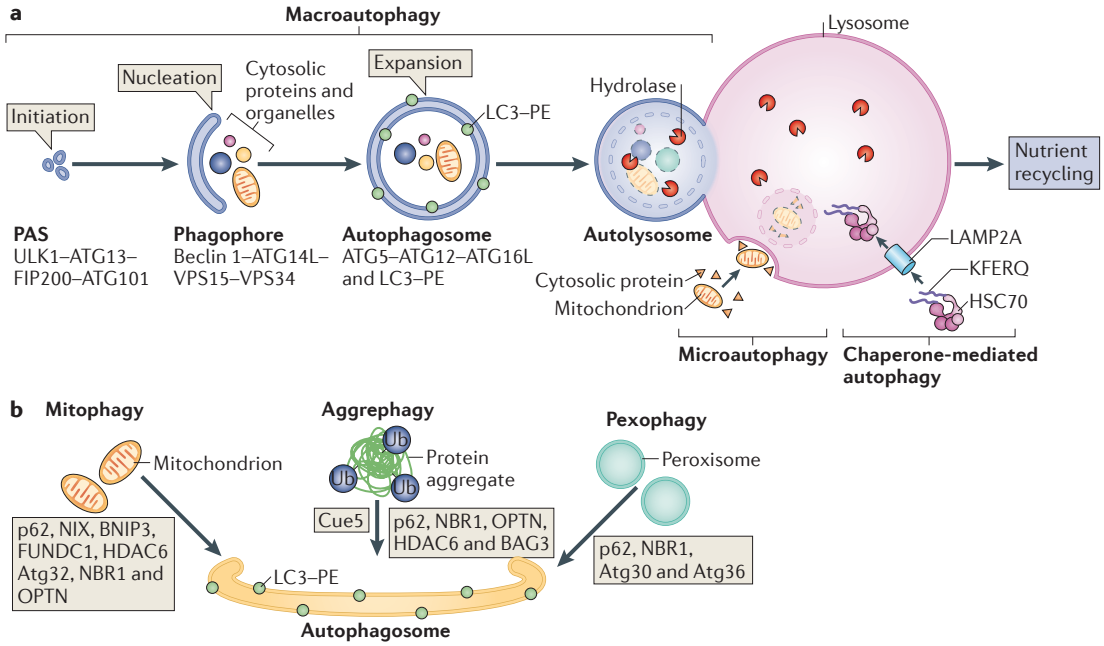

Figure 1 | **Overview of mammalian autophagy pathways. a** | In macroautophagy, initiation begins with the formation of the phagophore assembly site (PAS). This is mediated by the UNC51-like kinase (ULK) complex, which consists of ULK1 (or ULK2), autophagy-related protein 13 (ATG13), FAK family kinase interacting protein of 200 kDa (FIP200) and ATG101. Further nucleation requires the class III PI3K complex, which is composed of the vacuolar protein sorting 34 (VPS34) PI3K, along with its regulatory subunits ATG14L, VPS15 and beclin 1 (Atg6 in yeast). Phagophore membrane elongation and autophagosome completion requires two ubiquitin-like conjugation pathways. The first produces the ATG5–ATG12 conjugate, which forms a multimeric complex with ATG16L, whereas the second results in the conjugation of phosphatidylethanolamine (PE) to LC3 (the microtubule-associated protein 1 light chain 3, a principal mammalian homologue of yeast Atg8). PE-conjugated LC3 (LC3–PE) is required for the expansion of autophagic membranes, their ability to recognize autophagic cargoes and the fusion of autophagosomes with lysosomes. The resulting autophagosome fuses with endocytic and lysosomal compartments, ultimately leading to formation of the autolysosome. In microautophagy, substrates are directly engulfed at the boundary of the lysosomal membrane. In chaperone-mediated autophagy, substrates with the pentapeptide motif KFERQ are selectively recognized by the heat shock cognate 70 kDa protein (HSC70) chaperone and translocated to lysosomes in a LAMP2A-dependent manner. In all three processes, the autophagic cargo is degraded via lysosomal hydrolases. **b** | The selective autophagy of proteins and organelles is mediated by autophagy cargo receptors (listed within rectangles in the figure), which interact with both the autophagic substrate and the developing autophagosome via an LC3-interacting region (LIR). BAG3, BAG family molecular chaperone regulator 3; BNIP3, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3; FUNDC1, FUN14 domain-containing protein 1; HDAC6, histone deactylase 6; NBR1, next to *BRCA1* gene 1 protein; NIX, NIP3-like protein X; OPTN, optineurin; Ub, ubiquitin.

In addition to protein aggregates, selective autophagy is an important mechanism for the degradation of organelles. For example, damaged and superfluous mitochondria are targeted to autophagosomes in a process termed mitophagy[24,25]. Numerous studies have led to the identification of mitophagy receptors such as Atg32 in yeast, as well as BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), NIP3-like protein X (NIX) and FUN14 domain-containing protein 1 (FUNDC1) in mammals[26–33]. These receptors all possess an LIR motif to directly target mitochondria to autophagosomes. In addition, phosphorylation of these receptors is one mechanism to regulate mitophagy. For example, phosphorylation of Atg32 at residue serine 114 is necessary for its interaction with the adaptor protein Atg11, which recruits core ATGs to form autophagosomes that engulf mitochondria[34]. Similarly, the phosphorylation of serine residues flanking the LIR motif of BNIP3 promotes the binding of BNIP3 to LC3B and Golgi-associated ATPase enhancer of 16 kDa (GATE16; another Atg8 orthologue), thus facilitating mitophagy[35]. By contrast, dephosphorylation of the LIR of FUNDC1 is required to promote mitophagy during hypoxia[33].

Mammalian cells also utilize ubiquitin-dependent pathways to remove mitochondria. PTEN-induced putative kinase 1 (PINK1) is a mitochondrial protein kinase that accumulates on the outer membrane of depolarized mitochondria, which subsequently leads to the recruitment of the ubiquitin E3 ligase parkin and the polyubiquitylation of mitochondrial outer membrane proteins. Although p62 can recognize and cluster these ubiquitylated proteins, it remains unclear whether these aggregates are necessary for parkin-mediated mitophagy. Further details regarding the PINK1–parkin pathway in mitophagy are discussed elsewhere[25].

Molecular insight into the selective autophagic degradation of peroxisomes, termed pexophagy, originally came from studies of methylotrophic yeasts, such as *Pichia pastoris*. Two pexophagy receptors — Atg30 and Atg36 — have been identified in *P. pastoris* and

Methylotrophic yeasts
A genera of yeast that can only use methanol as the sole source of carbon and energy.

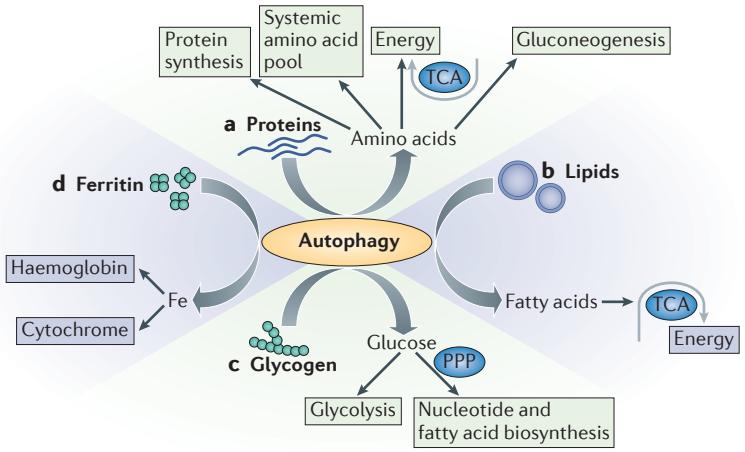

Figure 2 | **Autophagy-derived metabolites support diverse anabolic functions.** The autophagic degradation of proteins, lipids, glycogen and ferritin via autophagy enables multiple anabolic and biosynthetic pathways in cells. **a** | Under low nutrient conditions, autophagy-mediated protein catabolism results in the production of free amino acids that provide building blocks for protein synthesis and serve to maintain intracellular amino acid pools. These amino acids can also be converted to substrates that are utilized by the tricarboxylic acid (TCA) cycle for energy production or used as substrates for glucose production by gluconeogenesis. **b** | Fatty acids produced via lipophagy are converted into acetyl-CoA, which fuels the TCA cycle and energy production. **c** | Glycogen stores in liver and skeletal muscles are broken down to produce glucose that is utilized by glycolysis for energy (ATP) production as well as for the production of substrates, such as citrate, used for new lipid synthesis. In addition, glucose is diverted into the oxidative pentose phosphate pathway (PPP), a side branch of glycolysis important for nucleotide and fatty acid biosynthesis as well as the antioxidant response. **d** | Iron released from ferritin stores is utilized for the synthesis of metalloproteins such as haemoglobin and cytochromes.

Midbody
An intercellular bridge connecting the two dividing cells at the end of cytokinesis that functions to localize the site of abscission.

Midbody ring
A densely ubiquitylated ring-like macromolecular assembly of several proteins located at the midbody during the telomeric phase of cytokinesis.

mTOR–autophagy special coupling compartment
(TASCC). A recently discovered membrane compartment that is adjacent to Golgi apparatus. The TASCC is highly enriched for both mTOR and autolysosomes and promotes the synthesis of secretory proteins.

Glomerular podocytes
Highly specialized epithelial cells in kidney that are terminally differentiated and serve as an important component of the glomerular filtration barrier.

Saccharomyces cerevisiae, respectively[36,37]. In mammalian cells, pexophagy requires the autophagy cargo receptors p62 and NBR1, which recruit LC3-positive phagophores to monoubiquitylated peroxisomes[38,39].

In contrast to the turnover of mitochondria and peroxisomes, the precise role of selective autophagy receptors in the degradation of other organelles, such as ribosomes, nuclei and ER, remains unclear. However, notably, a recent study in *S. cerevisiae* reported that the degradation of ER is topologically equivalent to microautophagy but is not dependent on any genetic components of the core autophagy machinery or microautophagy machinery[40]. Selective autophagy can also target large macromolecules, such as lipids and iron complexes (see below), as well as intracellular pathogens (via a process termed xenophagy) and transient macromolecular structures within cells, such as the inflammasome, midbody and midbody ring[41–44].

Autophagy in energy metabolism

Although traditionally autophagy has been thought to break down cellular proteins during starvation, recent evidence suggests that it is active under basal, nutrient-rich conditions[45]. Furthermore, autophagy can mobilize diverse cellular energy stores such as carbohydrates, lipids and ferritin to replenish metabolites during both normal and stressed conditions (FIG. 2). In this section, we discuss how the diverse cellular constituents targeted via autophagy contribute to energy production and biosynthesis.

Protein catabolism. Early evidence that proteins are degraded by autophagy came from studies using hepatocytes isolated from perfused rat liver; these studies demonstrated that nutrient starvation increased the rate of protein degradation, accounting for ~4–5% of the total protein pool per hour versus 1.5% per hour under basal conditions[46,47]. More direct evidence that autophagy degrades proteins was gathered from multiple studies in yeast and mammals, in which the genetic ablation of autophagy decreased protein turnover[1]. These studies also showed that autophagy-mediated protein degradation sustains amino acid pools and protein synthesis in starving cells (FIG. 2). For example, in yeast, autophagy directly contributes to the intracellular amino acid pool because autophagy-incompetent cells (for example, Atg7-deficient mutants) are unable to restore amino acid pools following nitrogen starvation for just 3 hours[48]. Remarkably, the amino acids produced via autophagy are utilized for the synthesis of total proteins and probably the production of specific proteins, including Arg1p (arginino succinate synthetase for arginine biosynthesis) and heat shock protein 26 kDa (Hsp26p), both of which mitigate nitrogen depletion. Thus, the reduction in general protein synthesis due to diminished amino acid levels may further compromise the viability of autophagy-defective yeast mutants that are subject to prolonged nitrogen, carbon or sulfate starvation[48]. Autophagy also supports mitochondrial function in yeast cells by upregulating proteins involved in respiration and reactive oxygen species scavenging[49]. However, it is unclear whether autophagy-derived amino acid pools are used for the synthesis of these mitochondrial proteins that are crucial for yeast respiratory function.

Autophagy-derived amino acids are also important for enabling protein synthesis in mammalian cells. For instance, a defect in pre-implantation embryos was observed upon eliminating autophagy by genetically deleting *ATG5*; this defect was attributed to impaired protein recycling and protein synthesis owing to amino acid depletion[50]. Furthermore, in cells undergoing oncogene-induced senescence, autophagy contributes to amino acid flux via a specialized compartment termed the mTOR–autophagy special coupling compartment (TASCC), which is crucial for the enhanced synthesis of secretory proteins (BOX 2). Remarkably, TASCC formation has been observed in normal cells, such as glomerular podocytes, although the exact biological function of this compartment remains unclear[51]. Together, these studies illustrate how the catabolic functions of the autophagy pathway can be coupled to protein synthesis to sustain cellular function and viability.

In addition to maintaining protein synthesis, autophagy-mediated protein degradation is an important mechanism for producing energy (ATP) in response to stress (FIG. 2). Seminal studies showed that *Atg5*$^{-/-}$ and *Atg7*$^{-/-}$ neonatal mice exhibited reduced plasma levels of essential amino acids and branched-chain amino acids in different tissues[3,52]. This systemic insufficiency in branched-chain amino acids correlated with increased activity of AMP-activated protein kinase (AMPK)

Box 2 | **Autophagy and secretion**

Although autophagy is traditionally viewed as an autodigestive process, intriguing connections between the autophagy pathway and protein secretion are becoming increasingly appreciated. Studies have primarily focused on autophagy in unconventional secretion, a collection of processes through which certain proteins are secreted from cells either via direct trafficking from the endoplasmic reticulum (ER) to the plasma membrane in a Golgi-independent manner, or via the transport of cytoplasmic proteins lacking an amino-terminal ER signal sequence to the cell surface, completely bypassing the ER–Golgi route[126]. Autophagy-related proteins (ATGs) have been genetically implicated in the unconventional secretion of the acyl-CoA-binding protein Acb1 in yeast (AcbA in *Dictyostelium discoideum*), and inflammatory mediators such as interleukin-1β (IL-1β) and IL-18, the high mobility group protein B1 (HMGB1) and the integral membrane protein ΔF508 CFTR (cystic fibrosis transmembrane conductance regulator) in mammalian cells[127–131]. The unconventional secretion of these proteins is also dependent on Golgi membrane-binding proteins of the GRASP family in both yeast and mammals[129,130,132].

The molecular details of the unconventional secretion pathway are only beginning to emerge, and numerous questions remain unanswered regarding the role of autophagy. First, although genetic interconnections between ATGs and Grh1, the yeast GRASP orthologue, exist in *Saccharomyces cerevisiae*, recent research questions whether autophagy and Grh1 truly converge on a common secretory intermediate[133]. Second, although the early autophagosome-forming core machinery appears to be genetically required for unconventional secretion, it is unclear how the molecules to be secreted, such as Acb1 or CFTR, are actually incorporated into autophagosomes. Third, it is uncertain whether the autophagosomes are transported directly to the cell surface for secretion or whether they fuse with endocytic pathway components such as the multi-vesicular body (MVB). Because studies suggest that the exocytosis of MVBs can mediate the transport of intracellular cargo directly to the cell surface, the latter model seems the most plausible[134]. Indeed, early evidence suggests that the autophagy machinery may intersect with the endosomal sorting complexes required for transport (ESCRT) machinery to promote multiple MVB-associated functions, including exocytosis. For example, an ATG12–ATG3 complex interacts with the ESCRT-associated protein ALIX (also known as programmed cell death 6-interacting protein) to control MVB distribution, late endocytic trafficking and exosome biogenesis[135]. Finally, it remains obscure how secreted proteins potentially trafficking through autophagosomes are diverted away from lysosomes, or if autophagosome–lysosome fusion does occur, how the secretory cargo is protected from destruction via lysosomal hydrolytic enzymes.

In addition to unconventional secretion, components of the autophagy pathway have been genetically implicated in the regulated secretion of insulin, lysozymes, melanosomes, mast cell mediators and the contents of secretory lysosomes[136]. Furthermore, ATGs promote the efficient secretion of cytokines during oncogene-induced senescence and during cancer cell invasion[106,137]. Further dissecting the cellular mechanisms through which autophagy mediators facilitate these diverse secretory processes remains an important topic for future study.

in neonatal *Atg5*$^{-/-}$ mice, indicative of systemic ATP depletion. Because the metabolic products of branched-chain amino acids — acyl-CoA derivatives — are consumed by the tricarboxylic acid (TCA) cycle to create energy, autophagy-derived amino acids might be required to produce ATP during the neonatal starvation period.

Additional evidence that autophagy is important to produce amino acids came from studies using haematopoietic cell lines derived from *Bax*$^{-/-}$ *Bak*$^{-/-}$ mice[53]. These cell lines require interleukin-3 (IL-3) for the uptake of amino acids and nutrients from the external milieu. Upon IL-3 withdrawal, autophagy becomes crucial for energy production and cell viability; the concurrent inhibition of autophagy elicited a rapid decline in cellular ATP levels and profound cell death. However, both cell viability and ATP levels were restored upon the addition of methylpyruvate, a cell permeable TCA substrate; this result suggests that the amino acids released by autophagy in these cells are converted to substrates for energy production by mitochondria. Similar results were observed in primary mouse haematopoietic stem cells following metabolic stress due to cytokine withdrawal *in vitro* or nutrient starvation *in vivo*[54]. In addition, recent studies using liver-specific *Atg7*-null mice demonstrated that hepatic autophagy is critical for maintaining systemic blood glucose levels during fasting by converting autophagy-derived amino acids to glucose via hepatic gluconeogenesis[55]. Overall, these studies highlight the diverse functions of autophagy-derived amino acids in sustaining energy production via the TCA cycle and producing substrates that fuel gluconeogenesis.

The contributions of autophagy to tumour metabolism have been recently reviewed[56–58]. Similar to normal cells, tumour cell autophagy recycles macromolecules for amino acid synthesis and mitochondrial metabolism to support growth and survival[59]. Notably, a recent cellular proteomics study provided further insight into the role of autophagic proteolysis in tumour cell metabolism and survival. In Ras-mutant cancer cells subjected to metabolic stress, autophagy selectively targeted toxic or non-essential proteins for degradation, but excluded essential proteins that are necessary for maintaining autophagy and surviving stress. These results suggest that autophagy-mediated proteolysis remodels the proteome towards cellular pathways required for cell viability[60]. Finally, another major contribution of autophagy-mediated protein degradation is to remove aggregated or dysfunctional proteins to maintain the quality of intracellular proteins (BOX 1).

Transcriptional regulation of lipophagy. The discovery that intracellular lipid stores are degraded via autophagy has expanded our understanding of this catabolic process. During nutrient starvation, lipid droplets are hydrolysed to release free fatty acids for mitochondrial oxidation. The ability of autophagy to selectively degrade lipids is termed macrolipophagy (or lipophagy) and was first observed in hepatocytes[42]. Both *in vitro* and *in vivo* studies have demonstrated the accumulation of triglycerides and cholesterol when autophagy is genetically ablated[42]. Lipophagy also removes excess lipids to maintain basal lipid levels in liver cells (FIG. 3). The free fatty acids released by autophagy are used for β-oxidation and the TCA cycle to produce energy (FIG. 2). Importantly, acute challenge with a lipid stimulus negatively affects autophagic flux in cultured cells and mice, presumably because the increased intracellular lipid content diminishes autophagosome–endolysosomal fusion or suppresses the acidic and hydrolytic activity of lysosomes[61,62]. Hence, reduced hepatic macroautophagy due to excess lipid overload — for example, in obesity — exacerbates lipid accumulation *in vivo* and creates a vicious cycle that promotes hepatic ER stress and insulin resistance[63]. In support of this, reduced lipophagy in *Atg7* haploinsufficient mice is a possible cause of progression from obesity to diabetes because increased lipid toxicity promotes insulin resistance[64].

Gluconeogenesis
A process of glucose production by the metabolism of non-carbohydrate substrates such as pyruvate, lactate, oxaloacetate, glucogenic amino acids or fatty acids.

β-oxidation
The breakdown of fatty acids in the mitochondria into two carbon units of acetyl-CoA, which enter the citric acid cycle, and NADH and FADH2.

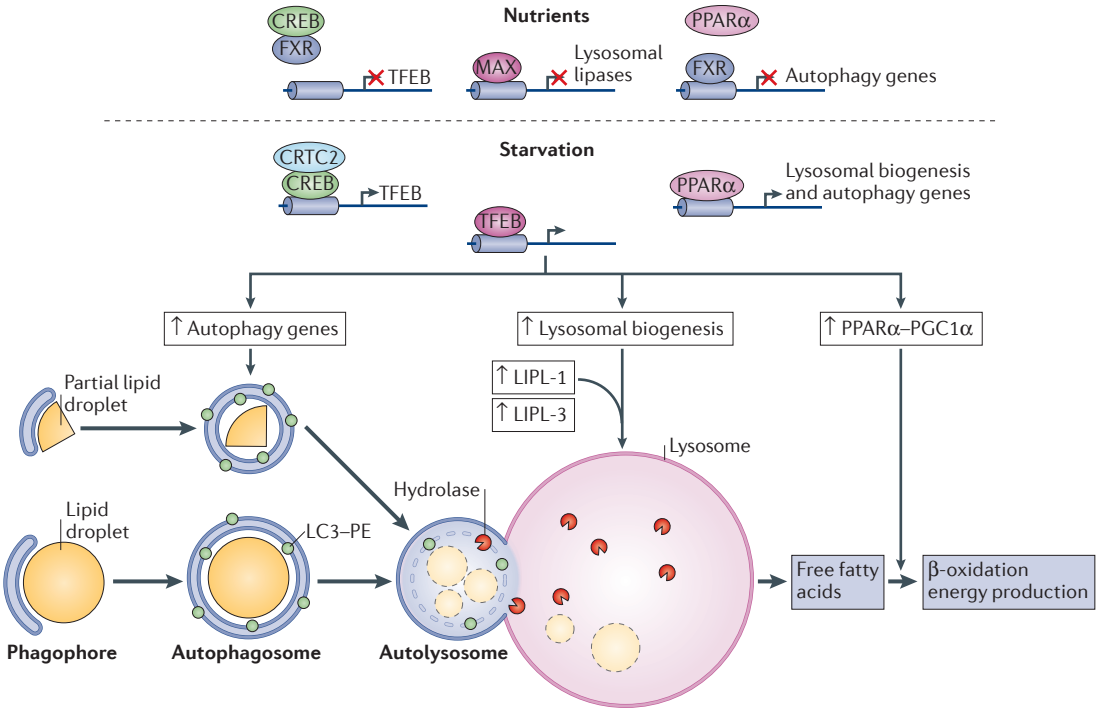

Figure 3 | **Transcriptional control of lipophagy.** During nutrient starvation, autophagy selectively degrades lipid droplets, a process termed lipophagy, by either sequestering a portion of larger droplets within LC3–phosphatidylethanolamine (LC3–PE)-bound phagophore membranes or by completely engulfing small lipid droplets. In the presence of nutrients, lipophagy is transcriptionally repressed by farnesoid X receptor (FXR), which inhibits the transcriptional activity of cAMP response element-binding protein (CREB) by disrupting the formation of a complex between CREB and its co-activator CRTC2; this complex is required for the transcription of TFEB (transcription factor EB), the protein product of which activates the transcription of autophagy and lysosomal biogenesis genes. FXR also competes with another nuclear receptor, peroxisome proliferator activator receptor-α (PPARα) for the binding sites in the promoter regions of autophagy genes. FXR specifically represses the transcription of autophagy genes; however, PPARα can activate the transcription of both autophagy and lysosomal biogenesis genes. Finally, in the presence of nutrients, MAX represses the transcription of lysosomal lipases. Upon starvation, FXR is inactivated, which allows PPARα to bind to the promoter of target genes and the CREB–CRTC2 complex to form and activate the transcription of TFEB, and consequently of TFEB target genes. Starvation also causes a switch from MAX-regulated transcription repression to TFEB-mediated transcription. MAX repressor is replaced by TFEB, which can further activate genes related to autophagy, lysosome biogenesis as well as the PPARα–PGC1α (PPARγ co-activator 1α) axis. Together, TFEB and PPARα support multiple processes favouring lipid catabolism, including autophagosome formation (by enhancing the expression of autophagy genes); lysosomal biogenesis to promote the degradation of autophagic cargo; the transcription of lysosomal lipases such as LIPL-1 and LIPL-3; and the activation of transcriptional programmes driving lipid catabolism in the cytosol (most notably, the TFEB-mediated activation of the PPARα–PGC1α axis).

Macrolipophagy is not limited to hepatocytes; it also occurs in fibroblasts, endothelial cells, lymphoblasts, dendritic cells, glial cells and neurons, suggesting that autophagic lipid degradation is important in diverse cell types[65–67]. Moreover, macrolipophagy has been reported in yeast, in which the degradation of lipid droplets is thought to support cell viability under carbon starvation. In yeast, the core autophagy proteins are involved in the degradation of lipid droplets and the process is distinct from other selective autophagy processes[68].

Before the discovery of lipophagy, the lysosomal compartment was principally thought to affect intracellular lipid pools by clearing lipoproteins endocytosed from the external environment. It is now evident that intracellular lipid droplets are broken down by the acidic lipases in lysosomes, a function that was previously attributed to cytosolic and ER lipases[69,70]. The importance of acidic lipases in lipophagy is further supported by recent studies in *Caenorhabditis elegans*, in which the transcriptional upregulation of the lysosomal lipases LIPL-1 and LIPL-3 was observed in response to starvation. Two transcription factors, MXL-3 and HLH-30, compete for binding to the promoter region of *lipl-1* and *lipl-3* genes; during nutrient starvation, HLH-30 overrides the transcriptional repressor MXL-3 to promote lipase expression[71]. Importantly, HLH-30 is the worm orthologue of the mammalian nutrient-sensitive transcription factor EB (TFEB), which simultaneously induces both autophagy and lysosomal genes during starvation[72]. Thus, the transcriptional activity of HLH-30 reinforces the upregulation of autophagy, lysosomal and lipolytic genes that are required for maintaining the supply of free fatty acids and glycerol for energy production[72]. Moreover, the deletion of *Tfeb* in mouse liver causes the accumulation of lipid droplets

after 24 hours of fasting, which is indicative of defects in intracellular lipid degradation[73]. Nevertheless, with regard to lipophagy, TFEB clearly possesses functions beyond its role as a master regulator of the autophagy–lysosomal axis; notably, TFEB also promotes the activation of peroxisome proliferator activator receptor-γ (PPARγ) co-activator 1α (PGC1α), a transcription factor that promotes lipid catabolism[73]. A complementary mechanism to regulate lipid degradation involves the nuclear receptor farnesoid X receptor (FXR; also known as the bile acid receptor), which competes with PPARα for binding to shared sites in the promoter regions of autophagy genes; when bound to the promoters of autophagy genes FXR represses their transcription in fed cells to inhibit lipophagy[74]. FXR can also inhibit the formation of a complex between the transcriptional activator cAMP response element-binding protein (CREB), which is active under conditions of fasting, and its co-activator CRTC2 to inhibit lipophagy in the liver of fed mice[75]. Collectively, these studies highlight the complexity of integrated transcriptional networks in fine-tuning lipophagy.

How lipids are selectively targeted for autophagy remains a topic of active investigation. Although LC3 may be directly recruited to lipid droplets to initiate the formation of a limiting membrane, this idea is controversial[76]. SNARE (SNAP receptor) proteins that have been implicated in both autophagosome biogenesis and lipid droplet fusion may also facilitate macrolipophagy[77]. The identity of the receptors targeting lipids to autophagosomes remains unclear, but recent research has indicated that dynamin 2, a GTPase involved in membrane scission, favours the degradation of hepatic lipid droplets by promoting the maturation of the autophagic compartment[78]. The disruption of dynamin 2 results in enlarged autolysosomes. These autolysosomes exhibit excessive tubular extensions that are associated with impaired autophagic lysosome reformation, a process that is critical for promoting the recycling and maintenance of the lysosomal pool in cells undergoing autophagy[78].

Autophagy in adipogenesis and energy balance. Adipose tissue is the primary storage organ for energy in the form of lipid droplets. Traditionally, adipose tissue is classified into two types: white adipose tissue (WAT) and brown adipose tissue (BAT). WAT, which consists of unilocular white adipocytes, is a major site of fat storage from which energy is mobilized in the form of triglycerides during nutrient deprivation. BAT is composed of specialized multilocular adipocytes that have higher numbers of mitochondria than unilocular white adipocytes; the multilocular adipocytes are involved in dissipating energy as heat during cold- or diet-induced thermogenesis by promoting the β-oxidation of fatty acids[79]. Recently, a third type of adipocyte was identified; called beige or brite adipocytes, these are brown-like adipocytes that are found in WAT[80]. These beige cells mimic white fat cells in the basal state, but function in a similar manner to brown fat cells by upregulating the expression of thermogenic genes in response to thermogenic stimuli. Interestingly, beige cells possess a gene expression pattern distinct from either white or brown fat cells[80].

In adipose tissue, autophagy appears to be crucial for the efficient differentiation of both white and brown adipocytes, rather than macrolipophagy. The role of autophagy in white adipogenesis was first demonstrated in primary mouse embryonic fibroblasts derived from *Atg5*-deficient mice[81]. These mouse embryonic fibroblasts failed to undergo adipogenesis and developed smaller-sized lipid droplets compared to control fibroblasts when stimulated to undergo differentiation. Similarly, autophagy inhibition in 3T3-L1 pre-adipocytes resulted in reduced levels of markers of white adipocyte differentiation and transcription factors that promote such differentiation along with decreased triglycerides[81]. *In vivo* studies using adipocyte-specific *Atg7*-deficient mice also showed that autophagy supports WAT differentiation[82,83]. Specifically, this deletion resulted in lean mice regardless of whether they had been fed a regular or high-fat diet. This phenotype was probably due to increased energy expenditure and lipid elimination via increased β-oxidation in adipocytes; in support of this hypothesis, white adipocytes contain more mitochondria, which is suggestive of 'browning' of WAT. Together, these studies demonstrate a key role for autophagy in WAT differentiation.

Similarly, the genetic ablation of autophagy in myogenic factor 5 (MYF5)-positive cells, a progenitor population that differentiates into skeletal muscle and BAT, resulted in profound defects in BAT differentiation and function[84]. Nevertheless, these animals displayed increased energy expenditure and raised body temperature compared to control mice, which correlated with the appearance of beige adipocyte features in the inguinal WAT, a subcutaneous adipose tissue. These mice also exhibited reduced skeletal muscle differentiation and glucose intolerance, suggesting that autophagy ablation in specific tissues can broadly affect systemic energy and glucose homeostasis.

Recent studies of mice in which autophagy was selectively inhibited in skeletal muscle further illustrate how autophagy ablation in specific tissue systemically affects lipid metabolism and energy homeostasis; these mice exhibit increased glucose tolerance and insulin sensitivity, reduced adiposity and resistance to diet-induced obesity[85]. This phenotype arises from an increase in dysfunctional mitochondria due to impaired mitophagy in muscle cells, which results in the increased expression of a stress-induced mitokine, fibroblast growth factor21 (FGF21). Intriguingly, increased FGF21 has systemic effects as it increases β-oxidation, lipolysis and the browning of WAT, thereby promoting energy expenditure. This study also demonstrated that mice with autophagic ablation in hepatocytes showed a remarkable resistance to high-fat-diet-induced hepatic steatosis and exhibited improved glucose tolerance. This effect is probably due to an increase in lipid catabolism driven by high levels of FGF21. This result differs from earlier reports showing that the absence of intact autophagy in hepatocytes leads to insulin resistance[63]. Overall, these studies reveal that the targeted inhibition of autophagy in one tissue may affect distant tissues by non-cell autonomous pathways; for example, the production of endocrine factors such as FGF21.

Hepatic steatosis
The accumulation of fat in the liver.

Further support for the idea that tissue-specific autophagy modulates broader systemic physiology comes from studies of hypothalamic neurons, in which autophagy has been implicated in controlling food intake and energy balance by regulating hypothalamic lipid metabolism[66,86]. Mice lacking ATG7 specifically in orexigenic agouti-related peptide (AgRP) hypothalamic neurons exhibit reduced body weight, total body fat and food intake in response to fasting[66]. This is because AgRP-specific *Atg7* deletion alters the levels of key neuropeptides in these hypothalamic neuronal populations, which is proposed to control appetite and energy homeostasis *in vivo*. Moreover, during nutrient starvation, normal hypothalamic cells take up more free fatty acids and accumulate more triglycerides, which induces hypothalamic autophagy; the resulting autophagy-derived intracellular lipids promote AgRP expression. Overall, these results illustrate how autophagy-regulated lipid homeostasis in a single hypothalamic neuronal population can affect energy balance in the entire animal.

Autophagy has also been examined in another nutrient-sensing hypothalamic neuron, the pro-opiomelanocortin (POMC) neuron, which produces anorexigenic neuropeptides that inhibit food intake and promote energy expenditure[87]. Multiple studies have demonstrated that *Atg7* deletion in POMC neurons causes increased body weight owing to hyperphagia[87–89]. However, more recent research argues against a general role for POMC neuron-specific autophagy in the control of energy homeostasis. In contrast to the effects induced by *Atg7* deficiency, the genetic deletion of either *Atg12* or *Atg5* in POMC neurons does not promote weight gain or adiposity in mice on a regular diet, even though these neurons exhibit robust and complete autophagy ablation[90]. Furthermore, upon consuming a high-fat diet, mice lacking ATG12 in POMC-positive neurons exhibit accelerated weight gain, adiposity and glucose intolerance, whereas mice lacking ATG5 in POMC-positive neurons do not. These recent studies suggest that individual ATGs may affect POMC neuronal function via non-autophagic mechanisms, rather than via the autophagy-dependent control of lipid metabolism[90]. Nevertheless, because autophagy regulates lipid and energy homoeostasis in numerous tissues, further understanding how autophagy impacts lipid homeostasis during obesity remains an important topic for future investigation.

Carbohydrate metabolism. Glycogen represents the major form of stored glucose in the liver; autophagic degradation of glycogen represents a crucial mechanism to maintain glucose homeostasis in response to increased demand for this carbohydrate[91,92] (FIG. 2). In the newborn, the plasma levels of the hormone glucagon increase in response to neonatal hypoglycaemia, resulting in the mobilization of glycogen stores in hepatocytes[93]. Glycogen exists in two principal intracellular pools: the cytosol and the autophagic vacuole. The phosphorolytic degradation of glycogen in the cytosol is mediated by the enzyme glycogen phosphorylase, whereas the hydrolytic degradation of this polysaccharide occurs via acid glucosidases located within lysosomes[46]. The autophagy-mediated lysosomal degradation of glycogen releases a non-phosphorylated form of glucose that can be rapidly utilized by starving neonatal cells; this type of glycogen degradation has also been reported in adult animals in both cardiomyocytes and skeletal muscles. Most notably, *in vivo* analysis of transgenic GFP-LC3 mice subjected to starvation indicates that there is an increase in autophagosome biogenesis in glycogen-rich, fast-twitch extensor digitorum longus muscle fibres in comparison to oxidative slow-twitch soleus muscles; this result suggests a link between autophagy regulation and glucose metabolism in adult muscle[94]. However, the importance of glycophagy (that is, the autophagic degradation of glycogen) in energy homeostasis in adults remains unclear. Interestingly, ATG7 deficiency in adult mice causes the accelerated depletion of glycogen from liver (the major organ for glycogen storage) during fasting but not under fed conditions[95].

Alterations in glycophagy have been associated with various genetic myopathies such as Pompe disease, Danon disease, infantile autophagic vacuolar myopathy and drug-induced vacuolar myopathies caused by treatment with chloroquine or hydroxychloroquine[96] (TABLE 1). Among these, Pompe disease has been extensively studied in the context of autophagy. Pompe disease is caused by a deficiency in lysosomal α-acid glucosidase (GAA), which results in the impaired degradation of glycogen as well as swollen, dysfunctional lysosomes, phenotypes that are most apparent in cardiac and skeletal muscles. A secondary phenotype of impaired GAA activity is defective autophagosome–lysosome fusion in the muscle fibres of patients with Pompe disease. This defect might interfere with the delivery of GAA into the lysosomal compartment, which has important implications for disease pathogenesis and the efficacy of recombinant enzymatic therapy in patients with Pompe disease[97–99]. Overall, despite the profound accumulation of glycogen-containing autophagic and lysosomal vesicles in skeletal myopathies, it remains uncertain whether impaired glycophagy functionally contributes to muscle dysfunction. However, genetic studies using a *Drosophila melanogaster* model of chloroquine-induced myopathy demonstrate that glycophagy in skeletal muscle is dependent on the core autophagy machinery[100]. Interestingly, this study also revealed that the efficient degradation of glycogen requires both enzymatic (phosphorolytic) and autophagic (hydrolytic) machineries[100]. However, an important unanswered question is whether the lysosomal degradation of glycogen is coordinated with the enzymatic degradation of glycogen via glycogen phosphorylase to maintain glucose levels. Such coordination is hinted at by a recent study in which *Atg7*-deficient adult mice showed accelerated glycogen mobilization during fasting[95].

In addition to its role in glycogen degradation, autophagy appears to have additional effects on glucose homeostasis in animals. For example, the suppression of autophagy in genetic and dietary models of obesity reduced blood glucose levels despite

Orexigenic
A stimulant (drug or hormone) that increases appetite.

Hyperphagia
An abnormal increase in appetite for the consumption of food, which is frequently associated with a defect in hypothalamic function.

Phosphorolytic degradation
The addition of a phosphate group to a substrate that initiates its cleavage.

Extensor digitorum longus muscle fibres
An example of a type II, fast-twitch muscle that has the ability to contract quickly and strongly but gets fatigued very rapidly.

Soleus muscles
An example of a type I, slow-twitch muscle that contains more mitochondria than type II, fast-twitch muscles; type I muscles contract for longer periods of time than type II muscles.

Pompe disease
Also called glycogen storage disease type II, Pompe disease is caused by a defect in lysosomal acid α-glucosidase.

Danon disease
A glycogen storage disease caused by a mutation in the gene encoding lysosome-associated membrane protein 2 (LAMP2).

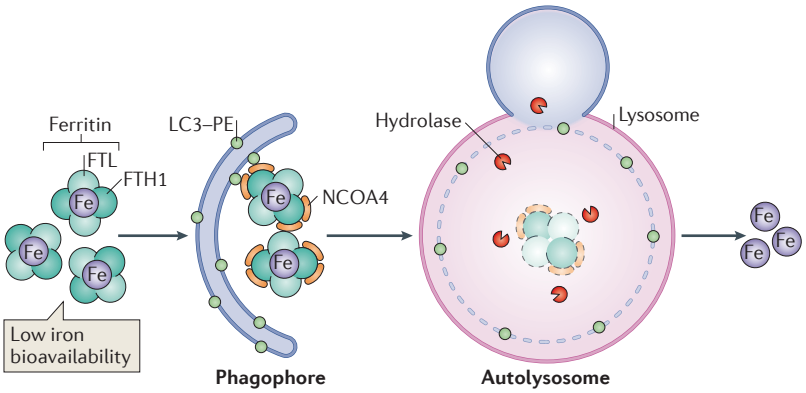

Figure 4 | **Ferritinophagy.** During conditions of low iron bioavailability in the cell, autophagy selectively degrades ferritin, an iron-containing protein complex, to mobilize bioavailable iron stores. This process is mediated by nuclear receptor co-activator 4 (NCOA4), an autophagy cargo receptor that binds ferritin heavy chain 1 (FTH1) and sequesters iron-containing ferritin complexes into autophagosomes by binding to microtubule-associated protein 1 light chain 3–phosphatidylethanolamine (LC3–PE) on the developing autophagosome membrane. Upon autophagosome maturation and fusion with the lysosome, both NCOA4 and ferritin are degraded, resulting in the release of bioavailable iron. FTL, ferritin light chain.

increased insulin resistance, possibly owing to impaired autophagy-mediated glycogen degradation[63]. Recent research using an inducible model of systemic *Atg7* ablation revealed a critical role for autophagy in the response of adult mice to starvation. Detailed metabolic analysis revealed that *Atg7* ablation causes a failure to mobilize serum-free fatty acids and initiates the rapid depletion of liver glycogen stores, resulting in low serum glucose levels and impaired metabolic fitness in starved animals[95]. Moreover, during exercise, autophagy is induced in cardiac and skeletal muscles, adipose tissue and pancreatic β-cells, which provides protection against glucose intolerance[101]. Similarly, in pancreatic β-cells, autophagy is important for maintaining glucose tolerance because mice lacking ATG7 in β-cells have reduced serum insulin levels and hyperglycaemia[102,103]. When these mice were fed a high-fat diet they exhibited reduced β-cell numbers and reduced insulin secretion[102]. In addition to crinophagy, a process involving the direct fusion of secretory granules with lysosomes, autophagy was thought to regulate the secretion of insulin-containing secretory granules to maintain stable insulin levels and thus indirectly contribute to glucose homeostasis[104]. Interestingly, a recent study has demonstrated that autophagy is suppressed in β-cells during starvation; starvation-induced nascent granule degradation occurs in these starved cells, resulting in a local increase of amino acids, thereby suppressing β-cell autophagy. Starvation-induced nascent granule degradation is positively regulated by inactive protein kinase D1 to suppress autophagy and prevent insulin release under nutrient-limiting conditions[105]. Finally, autophagy promotes glucose uptake and glycolytic flux in Ras-transformed mouse fibroblasts and breast cancer cells; however, it remains unclear whether autophagy similarly promotes intracellular glucose metabolism in oncogenic contexts beyond Ras[106].

Iron metabolism. The recent findings that autophagy promotes iron metabolism has further expanded our view of self-eating in mobilizing cellular nutrient stores (FIG. 2). Iron is required for countless biological processes, serving as a cofactor for several haem-containing and non-haem-containing proteins and enzymes. Excess iron is stored in ferritin, a large multisubunit molecule capable of chelating 2,000–2,500 atoms of iron per molecule[107]. Ferritin not only serves as the iron store for cells but also as a mechanism to prevent the generation of free radicals due to free iron. The regulation of iron levels is maintained in cells by a network of iron-dependent proteins; upon iron depletion, its bioavailability is maintained via release from ferritin. Initial studies using *Atg5*$^{-/-}$ fibroblasts revealed an important role for autophagy in ferritin degradation during iron depletion[108]. Subsequent ultrastructural studies in cells deficient in autophagy owing to the genetic deletion of either *FIP200* or *ATG9A* revealed the accumulation of ferritin cluster particles at the autophagosome formation site[109].

The mechanism by which ferritin is targeted for autophagic degradation has been clarified by two proteomic studies that identified nuclear receptor co-activator 4 (NCOA4) as a specific autophagy cargo receptor that binds ferritin and targets it for lysosomal degradation in a process termed "ferritinophagy". The newly identified function of NCOA4 as an autophagy cargo receptor is remarkably different from its originally identified roles as an androgen receptor co-activator[110]. Similar to known cargo receptors, NCOA4 is enriched in autophagosomes isolated from a human pancreatic cancer cell line[43]. In further support of its role as a receptor, NCOA4 was identified as an autophagy substrate when autophagy was inhibited using a highly selective chemical inhibitor of VPS34 (REF. 44). Biochemical studies indicated that NCOA4 interacts with the entire ferritin complex via ferritin heavy chain (FTH1) and colocalizes with ferritin in cells. Although NCOA4 lacks the canonical LIR motif found in other autophagy cargo receptors, the RNAi-mediated depletion of NCOA4 impaired the autophagic targeting and lysosomal-mediated degradation of ferritin, thereby implicating NCOA4 as a bona fide cargo receptor for ferritin turnover (FIG. 4). Moreover, the loss of NCOA4 reduced the level of bioavailable intracellular iron in cells subjected to iron depletion and led to the profound accumulation of iron in splenic macrophages *in vivo*[44]. Defects in ferritin turnover may cause the neurodegenerative disorder static encephalopathy of childhood with neurodegeneration in adults (SENDA), which is characterized by the accumulation of iron deposits in basal ganglia due to mutations in the autophagy gene WD repeat domain phosphoinositide-interacting protein 4 (*WDR45*)[111,112] (TABLE 1). Overall, these results highlight the importance of autophagy for iron homeostasis and bioavailability, especially during iron depletion.

Concluding remarks

Although autophagy is fundamentally regarded as a catabolic process, the studies overviewed here highlight the importance of this pathway in sustaining and even enabling anabolic pathways in certain settings. Indeed, autophagy-derived nutrients produced from the

Table 1 | **Effect of autophagy impairment in specific tissues and related pathologies**

Target tissue	Pathologies	Impaired autophagy type	Phenotype	Refs
Pancreatic β-cells, whole body (global haploinsuffiency)	Diabetes	Lipophagy, glycophagy, aggrephagy	Impaired insulin secretion, hyperglycaemia and accumulation of protein aggregates	64,102
Liver	Obesity	Lipophagy*, glycophagy	Insulin resistance, low blood glucose levels	63
Liver	Hepatic steatosis	Lipophagy	Increased lipid accumulation	42
Hypothalamus	Obesity	Hypothalamic lipophagy	Increased food intake, reduced energy expenditure	66,86,87
Skeletal, respiratory and cardiac muscle	Glycogen storage disease type II (Pompe disease)	Glycophagy	Accumulation of glycogen-filled lysosomes	138
Skeletal and cardiac muscle	Inherited myopathies	Glycophagy, aggrephagy	Accumulation of autophagosomes and glycogen	139
Liver	Deficiency in α1-antitrypsin	Aggrephagy	Accumulation of inclusions of insoluble enzyme α1-antitrypsin	121
Brain	Static encephalopathy in childhood with neurodegeneration in adulthood (SENDA)	Ferritinophagy	Iron accumulation in the globus pallidus and substantia nigra of the brain	111,112

*Current evidence suggests that the indicated autophagy type is impaired, but it has not been fully proven.

catabolic degradation of proteins, lipids, carbohydrates and ferritin all support diverse biosynthetic pathways, both during starvation and under basal conditions. Notably, because these anabolic functions are all intimately coupled to autophagy-mediated degradation in the lysosome, further understanding the regulatory mechanisms by which degradation products are exported out of the lysosomal lumen remains an important area for future study. In addition to its long-recognized role in autodigestion, non-canonical functions for the autophagy pathway in cellular synthetic functions are being increasingly appreciated, including, most notably, the autophagy-dependent control of protein secretion (BOX 2). As the autophagy-dependent secretion of cytokines and growth factors is likely to influence cell growth and function through non-cell-autonomous mechanisms, these findings have major biological implications. Hence, going forward, we will need to consider both autodigestive and non-canonical functions of autophagy to further ascertain how autophagy sustains core cellular and metabolic functions.

Further insight into how autophagy mobilizes various nutrient pools towards specific anabolic functions will also come from an increased understanding of selective autophagy in cells. Despite immense and exciting progress in this area of research, several aspects of selectivity remain unclear. For instance, the exact mechanisms directing the degradation of lipids in response to starvation must be further explored. Similarly, how glycogen pools are targeted by the autophagic machinery remains unknown, as does what determines the balance between the lysosomal and enzymatic degradation of glycogen. Finally, the recent discovery that NCOA4 is an autophagy receptor in the selective targeting of iron–ferritin complexes suggests that other selective targets for autophagy remain unidentified. Through the continued identification of new targets of autophagy and further dissection of the mechanisms of selectivity and metabolic pathways they support, we will gain new insight into how autophagy functions to sustain anabolism in both normal and diseased cells.

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Competing interests statement
The authors declare no competing interests.