Autophagy and metabolic homeostasis: Exploration in obesity-related metabolic diseases (Review)

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Abstract. Autophagy is an evolutionarily conserved catabolic process in which excessive nutrients, toxic protein aggregates, damaged organelles, and invading microorganisms in the cytoplasm can be isolated by the double-membrane structure of autophagosomes and delivered to lysosomes for degradation. Over the past two decades, research on autophagy has made significant progress. Autophagy not only plays a crucial role in maintaining intracellular homeostasis but also contributes to the development of various metabolic diseases. Metabolic imbalance of nutrients in obesity-related metabolic diseases can interfere with the autophagy process through a variety of mechanisms, resulting in further aggravation of the pathological damage of related organs. However, under certain conditions, inhibition of autophagy can have beneficial effects, thereby alleviating some of the harmful consequences of obesity. In this review, we will focus on the latest advances in the study of autophagy in obesity-related metabolic disorders, including type 2 diabetes, non-alcoholic fatty liver disease, and atherosclerosis. We will systematically discuss the definition and types of autophagy, the regulation of autophagy by nutrients, the imbalance of autophagy in obesity-related metabolic diseases and its molecular mechanism, and finally, we will summarize some drugs targeting the autophagy pathway.

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Contents

1. Definition and types of autophagy

Autophagy, a word derived from the Greek words ‘auto’ and ‘-phagy’, is a highly conserved physiological process in which eukaryotic cells degrade abnormal proteins and damaged organelles through the lysosomal system. In 1967, it was formally proposed by Professor Christian de Duve, winner of the Nobel Prize in Physiology or Medicine, while studying the effect of glucagon on rat liver lysosomes (1). After nearly 60 years of in-depth research, autophagy has been confirmed to be involved in the occurrence and development of a variety of diseases, such as cancer, cardiovascular diseases, metabolic diseases, and neurological diseases (2-5).

Autophagy can be divided into three main types based on the mechanism of substrate transport to lysosomes: Macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). Macroautophagy is a highly conserved mechanism of lysosomal degradation. Unlike microautophagy or CMA, macroautophagy requires the formation of double-layer membrane vesicles, which can isolate intracellular components such as proteins, macromolecular complexes, and organelles, and even invading pathogens (6).

Microautophagy is a conserved degradation pathway in which cytoplasmic components are directly engulfed and degraded by the lysosomal system. In yeast, this process is accomplished by direct invagination of the vacuolar membrane, whereas in mammalian cells, it is mediated by endolysosomes (7). The degradation substrates of microautophagy include soluble proteins and various organelles, such as peroxisomes, mitochondria, and even some nuclear structures (8). Finally, CMA is a particular protein degradation pathway. In this process, the cytoplasmic chaperone protein heat shock protein family A (Hsp 70) member 8, also know as heat shock cognate 70 (Hsc70) recognizes the pentapeptide motif (similar to the KFERQ sequence) in the substrate protein to form a substrate/chaperone protein complex, which binds to lysosome-associated membrane protein 2A (LAMP2A) on the lysosomal surface, triggering LAMP2A polymerization to create a transport complex. After the substrate is unfolded, the complex mediates the internalization of the substrate into the lysosome for degradation (9,10). However, with the continuous advancement of autophagy research, Sahu *et al* (11) demonstrated that proteins containing KFERQ-like motifs can also be degraded via an alternative pathway, endosomal microautophagy (eMI). eMI operates independently of LAMP2A, and the delivery of its cargo proteins to late endosomes (LEs) is primarily driven by the endosomal sorting complex required for transport (ESCRT) machinery mediated by vacuolar protein sorting (VPS)4 and tumor susceptibility gene 101, thereby facilitating the conversion of LEs into multivesicular bodies (MVBs). The process is initiated by the recognition and binding of cytosolic KFERQ-motif-containing proteins by Hsc70, followed by electrostatic interaction between the cationic domain of Hsc70 and the endosomal membrane, which induces localized membrane invagination. Subsequently, the cargo proteins are transported to lysosomes for degradation (12,13). Owing to its highly selective degradation mechanism, eMI has emerged as a promising avenue with potential applications in targeted cancer therapy (14).

The origin of the autophagosomal membrane is a central, long-debated question in autophagy research. Currently, three main models have been proposed. These involve membrane sources from the endoplasmic reticulum (ER), mitochondria, and the Golgi apparatus. In recent years, ER-mitochondria contact sites have gained significant attention. Wilhelm Bernhard first observed these structures in rat hepatocytes using electron microscopy as early as 1952 (15). Research has shown that under starvation conditions, key components of the class III phosphatidylinositol-3-kinase (PI3KC3) complex [including autophagy-related protein 14-like protein (ATG14L), VPS34, Beclin 1, and VPS15] become enriched in mitochondria-associated membranes and may be recruited to ER-mitochondria contact sites during autophagy induction. At the same time, autophagy related (ATG)5, a marker of autophagosome formation, localizes to these contact sites until the autophagosome is formed (16). Walker *et al* (17) proposed the omegasome model for starved cells. This model features specific ER subdomains enriched in phosphatidylinositol-3-phosphate (PI3P; also known as PtdIns3P), called 'omegasomes' (17). These cup-shaped structures protrude from the ER membrane and serve as platforms for autophagosome formation. Double FYVE-containing protein 1 binds to PI3P through its FYVE domain and simultaneously localizes to the ER/Golgi membrane with its ER-targeting sequence (18). Autophagy-related proteins such as ATG5 then get recruited to these PI3P-rich regions. These regions create a local environment favorable for the curvature and expansion of the phagophore, or isolation membrane. The Golgi apparatus is also a significant source of autophagosomal membranes in mammals. Locke and Collins (19) initially observed this phenomenon in 1965 in developing fat body cells of invertebrates. Later research confirmed the involvement of the Golgi complex in early autophagy (20). During telophase, when the Golgi apparatus reassembles, Golgi-derived membranes appear around autophagosomes, suggesting these supply membrane material for autophagosome expansion. ATG9, the only known transmembrane ATG protein, is also associated with the Golgi and may help deliver membranes to autophagosome formation sites (20). Of note, these models are not mutually exclusive. They may play dominant roles in different cell types or under distinct physiological conditions. The modes of autophagosome formation can also be species-specific. In yeast, phagophore membranes form at a specific cytoplasmic site, the pre-autophagosomal structure, but such a structure is not evident in mammalian cells (21). In mammals, phagophore membranes mostly originate from the ER (22), gradually forming through interactions with other cytoplasmic membranes, such as the trans-Golgi network and LEs (18). Under certain conditions, membranes may also be derived from the nuclear envelope (23). Notably, the scarcity of transmembrane proteins in autophagosomal membranes means mammalian cells might still form autophagosomes through *de novo* lipid synthesis. Despite progress in understanding membrane sources, fully clarifying the formation mechanism of this organelle demands further exploration. Key questions remain regarding autophagosome formation. It is unclear whether basal and stimulus-induced autophagosomal membranes are identical, whether the membrane source depends on the type of stimulus, whether ER-contact is essential for autophagosome formation, and whether formation dynamics differ among membrane sources. Most of these aspects still require clarification.

2. Formation of autophagosomes

Autophagy is a process that consists of a series of molecular events that ultimately lead to the formation of autophagosomes. Autophagosomes engulf cytoplasmic material and ultimately fuse with lysosomes to degrade their contents. Each step is regulated by a series of ATG proteins, many of which are organized into large complexes that are recruited in a specific order and whose activity is directly or indirectly regulated by metabolic signaling pathways. Next, the complexes formed during autophagy and the roles of the molecules within these complexes during autophagy are briefly introduced (24) (Fig. 1).

Autophagy initiation. First, autophagy initiation is associated with the Unc-51 like autophagy activating kinase (ULK) complex, which consists of ULK1, ATG13, RB1-inducible coiled-coil 1/focal adhesion kinase family interacting protein of 200 kDa (FIP200), and ATG101, and

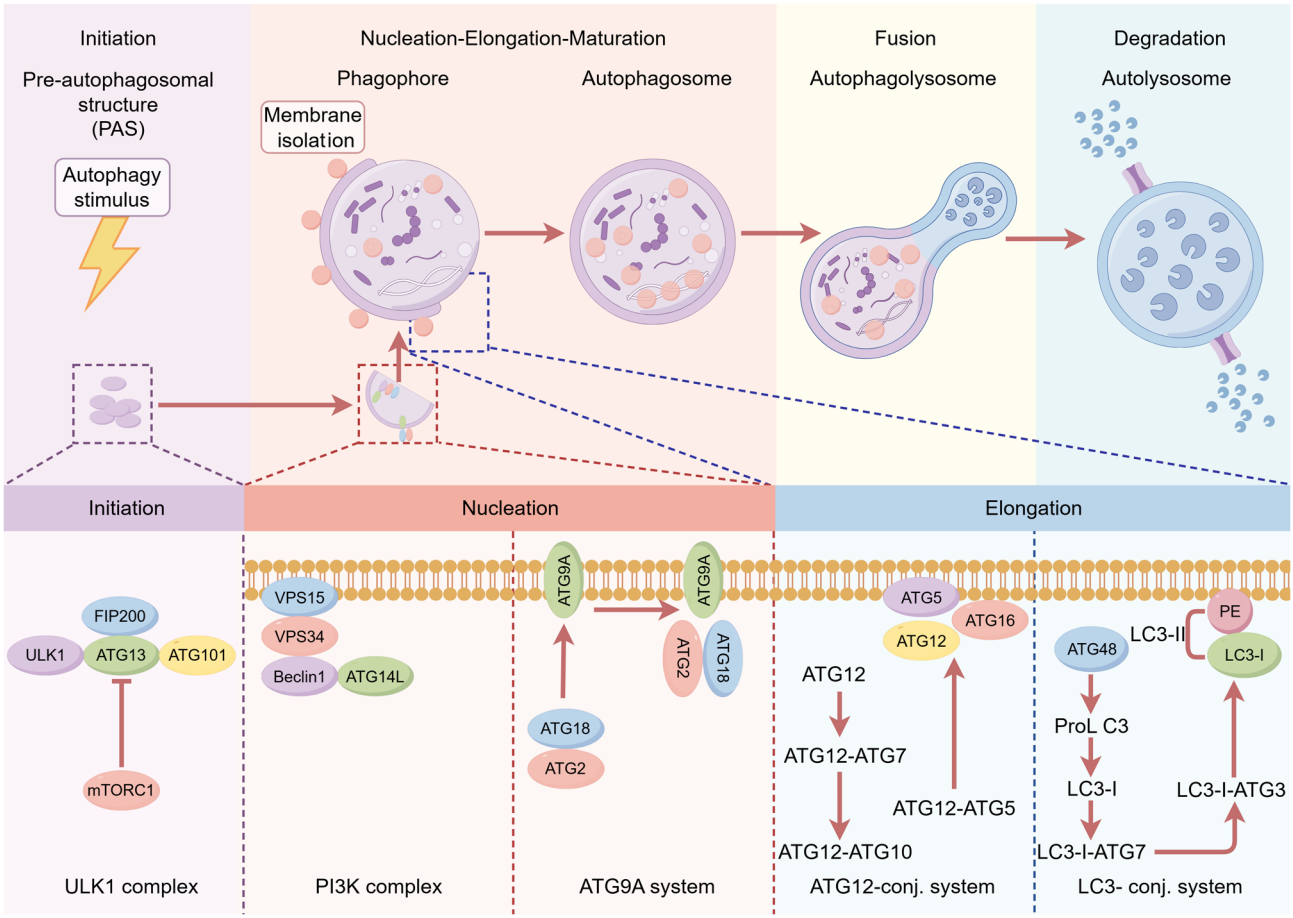

Figure 1. Autophagosome complex during the process of autophagy. FIP200, focal adhesion kinase family interacting protein of 200 kDa; ULK, Unc-51 like autophagy activating kinase; ATG, autophagy related; mTORC1, mechanistic target of rapamycin complex 1; VPS, vacuolar protein sorting; LC3, microtubule-associated protein 1A/1B light chain 3B; PE, phosphatidylethanolamine; SQSTM1, sequestosome 1; PI3K, phosphatidylinositol-3-kinase; HOPS, homotypic fusion and vacuole protein sorting.

its activity is negatively regulated by mechanistic target of rapamycin complex 1 (mTORC1) and positively regulated by AMP-activated protein kinase (AMPK) (25). Activation of this complex triggers membrane nucleation. As one of the key components of the complex, ULK1 is a serine/threonine protein kinase. The N-terminus of ULK1 contains a protein kinase domain, and the C-terminus is responsible for interacting with the C-terminus of ATG13, which is necessary for initiating autophagy (26). ATG101 is entirely composed of the Hop1, Rev7, Mad2 (HORMA) domain. It forms a heterodimer with ATG13 through the HORMA domain at its N-terminus, thereby preventing proteasomal degradation of ATG13 and enhancing the interaction between ATG13 and ULK1 (27,28). ATG13 is located on the autophagic isolation membrane and plays a role in connecting ULK1 with the scaffold subunit FIP200 (29). FIP200 is a predicted large coiled-coil protein involved in scaffolding, and FIP200 is crucial for maintaining ULK1 kinase activity. In the absence of FIP200, autophagy is severely inhibited (30). Chu *et al* (31) found that in a cellular model investigating the regulation of autophagic initiation, linear ubiquitin chain assembly complex (LUBAC) and OTU deubiquitinase with linear linkage specificity (OTULIN) coordinately regulate autophagy initiation and autophagosome maturation by mediating linear ubiquitination and stabilization of ATG13. In OTULIN-knockdown cells, hyperubiquitinated ATG13 is recruited to phagophores and undergoes sustained expansion, thereby impairing autophagosome maturation (31). Thus, LUBAC and OTULIN are recognized as ubiquitin enzymes that regulate the ubiquitination and protein levels of ATG13 to govern autophagic initiation and maturation.

Membrane nucleation and autophagosome formation. Secondly, membrane nucleation requires the participation of PI3KC3-complex I (CI). The PI3KC3-CI complex is composed of the catalytic subunit VPS34/PIK3C3, VPS15/phosphoinositide-3-kinase regulatory subunit 4 (PIK3R4), Beclin 1 (BECN1), and ATG14L. The complex adopts a V-shaped model, where PIK3C3 and PIK3R4 form the right arm of the V shape and possess catalytic functions, while BECN1 and ATG14 form the left arm of the V shape and have regulatory functions. PIK3C3 contains a C2 domain, a helical domain, and a kinase domain. The C2 domain of PIK3C3 directly contacts the WD40 domain of PIK3R4, and this binding is crucial for the kinase activity of PIK3C3 and autophagosome formation (32,33). Beclin 1 serves as the core component of the PI3KC3-CI complex. The coiled-coil domain of Beclin 1 functions to assemble complexes containing distinct ATG14L and UVRAG, thereby regulating the activity of VPS34 (34). When the ULK1 initiation complex is activated in response to changes in the energy status of the body, ULK1 binds to and

phosphorylates Ser19 of ATG14, Ser249 of VPS34, and Ser15 (as well as other sites) of Beclin 1, leading to the activation of PI3KC3-CI and the production of PI3P (35,36). PI3P, as a marker on the isolation membrane, is essential for recruiting specific autophagic factors and membrane remodeling (37,38). A previous study has demonstrated that in a mouse model of colitis, nuclear receptor binding factor 2 (NRBF2) functions as a regulatory subunit of the ATG14-Beclin 1-VPS34 complex to restrict intestinal inflammation and apoptosis through positive regulation of macroautophagy/autophagy. NRBF2-deficient mice exhibited exacerbated colitis symptoms following dextran sulfate sodium challenge, revealing a novel mechanism by which NRBF2 modulates the autophagic complex to limit intestinal inflammation (39). Nevertheless, whether NRBF2-mediated regulation of autophagy exerts similar effects in other models of inflammatory disease remains to be further investigated.

Autophagosome elongation. After the PI3KC3-CI complex is activated, the extension of phagosomes and the formation of autophagosomes are accomplished through two ubiquitin-like protein binding systems, the ATG12 and ATG8 systems (40). In the ATG12 dimeric system, ATG7 and ATG10 couple ATG12 with ATG5. Subsequently, the ATG12-ATG5 complex binds to ATG16L1 and moves to the phagosome, forming the ATG12-ATG5-ATG16L1 ubiquitin-like protein complex (41,42). The PI3P-binding protein WIPI2 recruits the ATG12-ATG5-ATG16L1 complex to the phagosome, promoting the transition from phagosome initiation to phagosome expansion (43). In the ATG8 system, the homolog of microtubule-associated protein 1A/1B light chain 3B (LC3) generated by the proteolysis of ATG4 from ATG8 is then converted to LC3I. Subsequently, the E1 activating enzyme ATG7, the E2 binding enzyme ATG3, and the E3 connecting enzyme ATG12-ATG5-ATG16L1 activate LC3I and promote its interaction with phosphatidylethanolamine, forming lipidated ATG8/LC3-II (44-47), coordinating the extension of the phagosome. When the extended membrane closes around its cargo, ESCRT, including VPS37A, charged MVB protein 2A, and AAA ATPase VPS4, participates in the regulation of autophagosome closure (48-50). Additionally, it has been found that the ER-localized autophagy protein EPG-3/vacuole membrane protein 1 and transmembrane protein 41B also play a key role in controlling the maturation of phagosomes and autophagosome closure (51-53).

Liu *et al* (54) demonstrated that hypoxia-inducible factor-1α at the translational level (HITT) binds to the key autophagy protein ATG5, thereby preventing the formation of the ATG12-ATG5-ATG16L1 complex and suppressing autophagosome biogenesis. This sensitized colorectal cancer cells to PI-103-induced cell death both *in vitro* and *in vivo* (in a nude mouse model). The study identified HITT as a novel RNA-based regulator of autophagy (54). However, the structural basis underlying the HITT-ATG5 interaction and its upstream regulatory signals remain to be elucidated.

Autophagosome fusion with lysosome. The final step of autophagy is the fusion of the the autophagosome with the lysosome, resulting in the degradation of autophagic cargo by lysosomal hydrolases. A series of factors regulates this process. The roles of the homotypic fusion and protein sorting (HOPS) complex and the soluble NSF attachment protein receptor (SNARE) complex in autophagic fusion are examined (55,56). The HOPS complex is the core complex for autophagosome-lysosome fusion and consists of six subunits, including VPS11, VPS16, VPS18, VPS33A, VPS39, and VPS41 (57). In yeast, HOPS binds to the vacuolar Rab7-like GTPase Ypt7 through its subunits Vps41 and Vps39, and supports autophagosome-lysosome fusion by promoting SNARE assembly. VPS41 is a molecular ruler for membrane fusion mediated by HOPS (58). Additionally, the HOPS complex promotes autophagosome-lysosome fusion through interaction with (syntaxin 17) STX17. When VPS33A, VPS16, or VPS39 are knocked out, autophagic flux is blocked, leading to the accumulation of STX17 and LC3-positive autophagosomes (59). The SNARE complex is a major participant in controlling membrane-mediated transport through vesicle fusion and has been proven to be the core mechanism for autophagosome-lysosome fusion (60). SNAREs can be classified into Q-SNAREs and R-SNAREs, and Q-SNARE proteins are further divided into Q-a, Q-b, and Q-c SNARE proteins based on their amino acid sequences in the SNARE domain (61). Q-SNARE and R-SNARE proteins achieve membrane fusion by forming trans-SNARE complexes. For example, the QaSNARE protein STX17 is located in the autophagosome, while the R-SNARE protein vesicle-associated membrane protein 8 is located in the lysosome/LE. By recruiting Qbc-SNARE protein synaptic-associated protein 29 (SNAP29), they jointly form a trans-SNARE complex to achieve the fusion of the autophagosome and the lysosome (62). Using the inhibitor SM15, SNAP29 O-GlcNAcylation can be enhanced, inhibiting the formation of SNARE complexes and blocking the fusion of autophagosomes and lysosomes (63).

3. Regulation of autophagy by nutrients

Autophagy is highly sensitive to changes in the nutritional environment, cellular metabolism, energy status, hypoxia, oxidative stress, DNA damage, protein aggregation, and the presence of intracellular pathogens. Autophagy can be induced by the deficiency of essential nutrients (such as glucose and amino acids) or specific metabolites (such as fatty acids and ammonia). Therefore, a thorough understanding of the mutual regulation between autophagy and macronutrient concentrations is crucial for formulating strategies to combat obesity.

Amino acids. Amino acids, as the fundamental building blocks of proteins, play a crucial role in maintaining the environmental nutrient levels necessary for life. When the supply of amino acids is insufficient, proteins respond to cellular nutrient fluctuations by activating the ubiquitin-proteasome degradation and autophagy mechanisms (64). Conversely, when there is an accumulation of specific amino acids in cells, the accumulated amino acids induce autophagic dysfunction in cells and promote disease progression (65). Two evolutionarily conserved nutrient pathways, namely the mTORC1 pathway and the general control non-derepressible 2 (GCN2) pathway, play key roles in amino acid sensing (66,67).

mTORC1 senses amino acids through signal transduction. Under conditions of sufficient amino acids, amino acids activate Rag guanosine triphosphate (GTP)ases, promoting the translocation of mTORC1 to the lysosomal surface and regulating autophagy (68,69). Sciarretta *et al* (70) found that mice with high-fat diet (HFD)-induced obesity and metabolic syndrome exhibited dysregulated cardiac activation of Ras homolog enriched in brain and mTORC1 during ischemia. These HFD mice displayed suppressed cardiac autophagy, which further exacerbated myocardial ischemic injury. Pharmacological and genetic inhibition of mTORC1 restored autophagy and abolished the increase in myocardial infarct size observed in HFD mice (70). Under conditions of amino acid starvation, Nowosad *et al* (71) discovered that a fraction of p27 is recruited to lysosomes, where it interacts with late endosomal/lysosomal adaptor, MAPK and mTOR activator 1 (LAMTOR1). The binding of p27 to LAMTOR1 prevents Ragulator complex assembly and mTORC1 activation, thereby promoting autophagy. Conversely, p27-deficient cells exhibited elevated mTORC1 signaling, along with impaired lysosomal activity and autophagy. This phenotype is associated with the cytoplasmic sequestration of transcription factor EB (TFEB), which prevents the induction of lysosomal genes required for lysosomal function (71). Additionally, Wong *et al* (72) also found that during amino acid starvation, autophagy can be induced by promoting the dephosphorylation of ULK1. This occurs through the stimulation of the dissociation of protein phosphatase 2A from its inhibitor, Alpha4, which increases the phosphatase activity of ULK1 (72).

For the control of the GCN2 pathway, GCN2 is a serine/threonine protein kinase with a high affinity for all uncharged tRNAs. It senses the intracellular amino acid levels by binding to uncharged tRNAs (73). When the intracellular amino acid levels are low, GCN2 binds to specific uncharged tRNAs, triggering the homodimerization and autophosphorylation activation of GCN2. The activated GCN2 phosphorylates the eukaryotic translation initiation factor 2α at the Ser51 site, and this phosphorylation can upregulate the activation transcription factor 4 (ATF4) and C/EBP homologous protein, thereby inducing autophagy by enhancing the transcription of autophagy-related proteins (74). Disruptions in intracellular amino acid levels occur frequently in obesity-related metabolic diseases, and in these cases, autophagy dysregulation often occurs. However, the exact mechanism of 'resetting and/or reactivation of mTOR' remains unclear. Future research should further investigate the regulatory mechanism by which changes in amino acid levels affect the upstream molecules of mTOR (Fig. 2).

Glucose. As the primary energy source, glucose plays a central role in the metabolic processes throughout the body. Glucose not only generates energy through oxidative phosphorylation but also provides intermediate biomolecules, such as fatty acids, amino acids, and nucleotides, for biosynthesis according to the needs of cells. Glucose can affect the level of autophagy by regulating the secretion of glucagon and insulin. Glucagon can enhance autophagy, while insulin signaling inhibits autophagy (75,76).

High glucose (HG) inhibits autophagy through the AMPK pathway. For instance, Wang *et al* (77) found that when chondrocytes were treated with different HG concentrations, the AMPK signaling pathway and autophagy were significantly inhibited. At the same time, apoptosis-related and senescence-related markers were significantly upregulated. 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR) reversed these phenomena. This research indicates that HG can inhibit autophagy through the AMPK signaling pathway, leading to chondrocyte apoptosis and senescence (77). During glucose deficiency, ATP levels decrease, promoting the accumulation of AMP and the activation of AMPK. AMPK can inhibit mTORC1 activation of autophagy by stimulating the tuberous sclerosis complex (TSC)1-TSC2 (also known as hamartin-tuberin) complex or directly through the phosphorylation of the ULK1 complex (78). In agreement with this, Karabiyik *et al* (79) demonstrated that under glucose deprivation, AMPK activates ULK1, leading to phosphorylation of the lipid kinase PI3P-phospahte 5-kinase, type III (PIKFYVE) at Ser1548. The activated PIKFYVE subsequently promotes the formation of phosphatidylinositol-5-phosphate (PtdIns5P)-containing autophagosomes, thereby driving autophagy upregulation. This novel finding that ULK1 orchestrates a non-canonical autophagic pathway, PtdIns5P-dependent autophagy, not only expands our understanding of autophagy but also unveils potential therapeutic strategies for human diseases (80). Another key signaling molecule involved in glucose-mediated autophagy regulation is the forkhead box protein O (FOXO) family transcription factors. NAD^+-dependent sirtuins may deacetylate FOXO, thereby promoting autophagy (81,82). Future development of novel autophagy regulation strategies targeting the glucose-sensing pathway will provide potential therapeutic approaches for metabolic diseases related to obesity, such as diabetes, obesity, and cancer (Fig. 2).

Lipids. Lipids are a diverse group of nutrients that include fatty acids and cholesterol. They are characterized by their hydrophobic carbon backbone and are used for energy storage, membrane biosynthesis, and other cellular processes (83). Although increased lipid intake and lipid storage disorders (such as in the state of obesity) can lead to abnormal autophagy function of cells, compared to the interaction between autophagy and amino acids or glucose, the interaction mechanism between cell autophagy and lipids has not been fully elucidated. However, research has shown that saturated fatty acids and unsaturated fatty acids have a certain duality in regulating autophagy (84).

Excessive intake of saturated fatty acids can lead to the hypertrophy of fat cells and induce autophagy. Through research using an *in vitro* model of 3T3-L1 adipocytes in mice, it was found that high concentrations of palmitic acid (PA) would induce autophagy through ER stress. Using 4-benzoylbenzoic acid to block the ER stress pathway significantly reduced the level of LC3-II, and autophagy levels were inhibited (85). Additionally, in the study on the lipid toxicity effect of saturated fatty acids on brain astrocytes, it was discovered that after treating primary astrocytes with PA, the level of LC3-II (a marker of autophagosomes) increased. By contrast, the flux of LC3-II in astrocytes decreased, and the autophagy level of astrocytes was blocked (86). Compared with saturated fatty acids, unsaturated fatty acid oleic acid (OA) can also

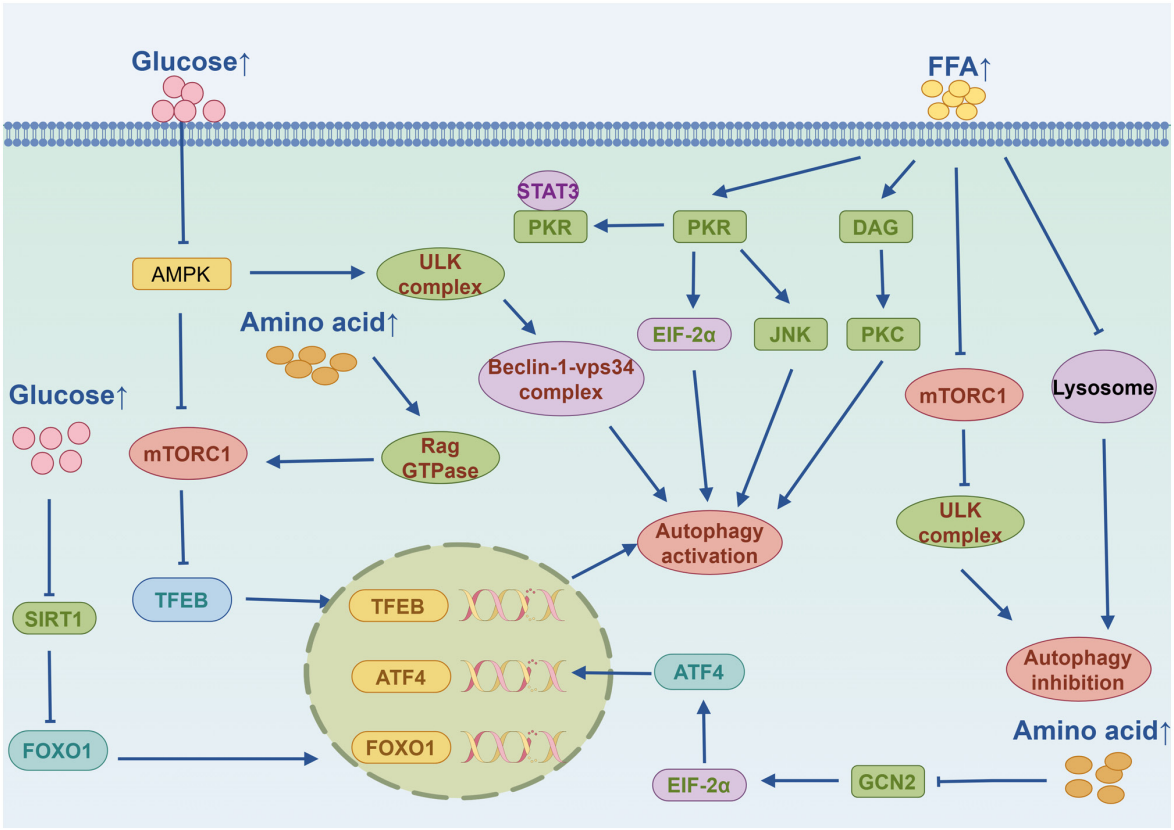

Figure 2. Regulation of autophagy by glucose, amino acids, and fatty acids. FFA, free fatty acids; PKR, portein kinase R; DAG, diacylglycerol; PKC, protein kinase C; EIF-2α, eukaryotic translation initiation factor-2α; VPS, vacuolar protein sorting; AMPK, AMP-activated protein kinase; mTORC1, mechanistic target of rapamycin complex 1; SIRT1, sirtuin 1; TFEB, transcription factor EB; ATF4, activation transcription factor 4; FOXO1, forkhead box O1; GCN2, general control non-derepressible 2; ULK, Unc-51 like autophagy activating kinase.

trigger autophagy, but the underlying molecular mechanism is different. The research by Niso-Santano *et al* (87) showed that OA may induce autophagy through a non-classical pathway. In this pathway, the LC3 protein related to autophagosomes (LC3-II) binds to the multi-protein PI3KIII class/VPS34 complex containing Beclin 1, thereby driving the autophagic process of the Golgi apparatus (87). Furthermore, in a mouse model of non-alcoholic fatty liver disease (NAFLD), it was demonstrated that PA induces autophagic impairment by reducing the nuclear translocation of TFEB and suppressing Cathepsin B activity. By contrast, OA markedly alleviated PA-induced apoptosis and autophagic dysfunction in hepatocytes, and improved hepatic glucose and lipid metabolism, indicating that OA-driven autophagy represents a key protective mechanism against NAFLD (88). Therefore, clarifying the regulatory mechanism of fatty acid metabolism on autophagy will provide novel intervention strategies for the treatment of obesity-related metabolic diseases (Fig. 2).

Tissue specificity and model differences in nutrient-mediated autophagy. The regulation of autophagy by nutrients exhibits significant tissue specificity, with notable differences in results among various research models. This phenomenon is particularly prominent in the sensing mechanisms of core nutrients such as amino acids, glucose, and lipids. Regarding the regulation by amino acids, a study in a mouse model of diabetic cardiomyopathy found that the deficiency of branched-chain amino acids could activate autophagy in cardiac fibroblasts through the AMPK-ULK1 signaling pathway, thereby exacerbating the cardiomyopathy phenotype in diabetic mice (89). However, Fermo *et al* (90) found in a rat cerebral cortex study that the supplementation of branched-chain amino acids could significantly increase the levels of autophagy markers Beclin 1, ATG7, and ATG5 in the cerebral cortex, enhance the expression of ATG12 in the striatum, and increase the levels of ATG5 and LC3-I/II in the hippocampus, thereby promoting autophagy in brain regions (90). These findings suggest that the regulation of autophagy by amino acids has clear tissue dependence. In terms of glucose regulation, Li *et al* (91) found that high blood sugar levels in colorectal cancer (CRC) cells could inhibit autophagy by activating the PI3K/AKT/mTOR pathway, thereby promoting the proliferation and migration of CRC cells (91). However, in the *in vitro* culture model of MC3T3-E1 osteoblast precursor cells, high blood sugar significantly induced autophagy through the reactive oxygen species (ROS)-AKT-mTOR axis, affecting the apoptosis and proliferation of cells (92), which exhibited a different regulatory pattern compared with the tumor cell model. In lipid regulation research, Hossain *et al* (93) found that free fatty acids (FFAs) could induce the upregulation of DEAD-box helicase 3 expression in HepG2 cells, thereby increasing miR-141, inhibiting sirtuin 1 (SIRT1) expression, and reducing the levels of autophagy-related proteins, ultimately decreasing autophagic flux (93). In a cell model of alcohol-related liver disease, FFA could downregulate LAMP2 expression through ATF4-mediated endoplasmic reticulum stress, damaging

autophagic flux, while overexpression of LAMP2 could restore autophagy function and alleviate alcohol-induced liver injury (94). In summary, the tissue specificity and model differences in the nutrient-autophagy regulatory axis essentially stem from the precise regulatory network formed by biological systems during evolution to maintain metabolic homeostasis in different tissues under specific physiological conditions. Future research should address the limitations of single-cell models and tissue types by establishing a comparative analysis framework that spans multiple tissues and models, thereby enabling a systematic investigation of dynamic changes in nutrient-sensing pathways under various physiological and pathological conditions. In-depth exploration in this direction will not only help clarify the heterogeneous pathogenesis of metabolic diseases but also provide a theoretical basis for the formulation of precise nutritional intervention strategies, that is, to design differentiated nutritional intervention plans based on the autophagy status of different tissues and disease stages to achieve precise regulation of autophagic activity.

4. Autophagy and obesity-related metabolic diseases

Given the complex interplay between nutrient metabolism and the autophagic process, it is reasonable to hypothesize that autophagy plays a critical role in the pathogenesis of obesity-related metabolic diseases. The pathological state induced by obesity is typically characterized by abnormal accumulation of lipid droplets, formation of protein aggregates, and mitochondrial damage, all of which are primary degradation substrates of the autophagic pathway. Consequently, impaired autophagy may accelerate the progression of obesity-related pathological alterations in multiple tissues. Based on this, the following discussion will further explore the intrinsic relationship between autophagy and obesity-related metabolic diseases, aiming to provide insights for future research and the development of therapeutic strategies.

Type 2 diabetes (T2D). T2D is mainly characterized by dysfunction of pancreatic β cells and insulin resistance. Obesity is considered a contributing factor to type 2 diabetes mellitus (T2DM), and the prevalence of T2DM increases with the increase in obesity prevalence (95). A recent study showed that autophagy plays a crucial role in maintaining the typical structure and function of pancreatic β cells and in mitigating insulin resistance in T2D (96). The mechanisms of autophagy in T2D are next examined.

Firstly, basal autophagy has been proven to be crucial in maintaining the typical structure and function of pancreatic β cells and in mitigating insulin resistance. Under conditions of insulin resistance induced by T2D or HFD, autophagic vacuole formation in early-stage β cells is markedly upregulated to clear the accumulation of various toxic intracellular aggregates. This increase in autophagic activity at an early stage serves as a distinctive protective defense mechanism (97). Furthermore, a study using an animal model investigating autophagic activity in pancreatic β cells revealed that ATG7-deficient mice exhibit impaired glucose tolerance and reduced serum insulin levels, along with β-cell morphological abnormalities including mitochondrial swelling, ER distension, and vacuolar changes (98). Additionally, under conditions of metabolic stress, Martino *et al* (99) established a tiered experimental model comprising INS-1E cells, isolated rat islets, and isolated human islets, and demonstrated that palmitate, as a representative FFA, consistently activates autophagic pathways across species, whereas HG treatment alone does not elicit this effect. Further investigations revealed that inhibition of autophagy exacerbates FFA-induced β-cell death (99). Collectively, these findings indicate that autophagy is an essential mechanism for maintaining β-cell structure and function, and that its dysfunction may lead to organellar metabolic abnormalities, impaired insulin secretion, and the onset of hyperglycemia. Furthermore, in a HFD-induced T2D model, Meng *et al* (100) observed in zebrafish that a lipotoxic environment induces autophagic deficits, disrupts insulin signaling, and leads to abnormal accumulation of preproinsulin, thereby compromising cellular homeostasis and promoting the development of insulin resistance. Concurrently, Budi *et al* (101) reported in a C57BL/6 mouse model fed a HFD that chronic high-fat feeding not only elicits insulin resistance but also results in late-stage autophagy inhibition, ER stress, and adipocyte apoptosis. The suppression of autophagy may indirectly contribute to the progression of insulin resistance by exacerbating ER stress and apoptotic cell death (101). Therefore, basal autophagy of pancreatic β cells appears to be an adaptive response and is crucial for the homeostasis of pancreatic β cells.

On the other hand, some studies have also reported the adverse effects of autophagy in T2D. Excessive activation of autophagy is associated with autophagic apoptosis and necrosis of pancreatic β cells. For instance, in pancreatic tissues isolated from rats, it was found that with age, the expression of autophagy markers LAMP2 and LC3b and the apoptotic index significantly increased in aged rats. Excessive activation of autophagy induced autophagic apoptosis of pancreatic β cells (102). Additionally, a case-control study of human pancreatic samples from patients with T2D and healthy controls showed that autophagosomes and autophagic vesicles were correlated with the level of β-cell death, and metformin improved the autophagic changes in diabetic β cells and delayed β-cell death (103). The known autophagy inhibitor mTOR plays a crucial role in preventing pancreatic β-cell apoptosis induced by oxidative stress and autophagy-mediated cell death. It limits insulin resistance and the development of T2D caused by pancreatic β-cell death (104). This indicates that autophagy has a detrimental effect on pancreatic β cells, leading to accelerated cell death and the development of T2D. However, numerous unanswered questions remain regarding the specific mechanisms that regulate pancreatic β-cell autophagy. Therefore, further elucidation of the mechanism of pancreatic β-cell autophagy dysregulation may provide novel therapeutic interventions for diabetes.

NAFLD. NAFLD is the most common liver disease worldwide and can progress to more severe non-alcoholic steatohepatitis (NASH), liver cirrhosis, and hepatocellular carcinoma. Notably, 70-80% of obese and diabetic patients will develop NAFLD (105). The pathogenesis of NAFLD involves multiple concurrent events. During this process, defective organelles, such as lipid droplets, mitochondria, ER, and peroxisomes, accumulate in the cells and require degradation systems such as autophagy to remove these harmful cellular components.

Previous research has demonstrated that autophagy disorders are closely related to NAFLD (106).

NAFLD is characterized by the irregular deposition of triglycerides in liver cells, mainly because the amount of fatty acids entering the cells through intake or synthesis exceeds the amount of fatty acids oxidized or excreted by the cells. Autophagy dysfunction is considered an important marker for the aggravation of fatty degeneration in NAFLD (107). In a HFD-induced NAFLD mouse model, it was found that the autophagic activity in the liver was downregulated in ATG7 gene-diminished autophagy-deficient mice, accompanied by an increase in fatty degeneration (108). It is notable that even under a regular diet, specific liver knockout of ATG7 in mice leads to the occurrence of hepatic fatty degeneration, indicating that autophagy plays a crucial role in preventing fat accumulation in liver cells (109). Consistent with these research findings, it was found that sequestosome 1 (SQSTM1) induces the phosphorylation of ULK1 by promoting the interaction between AMPK and ULK1, thereby inducing macroautophagy/autophagy. The activity of the non-classical KEAP1-NFE2L2 pathway mediated by SQSTM1 conferred protection to the liver, protecting it from the effects of lipid toxicity in the liver of SQSTM1-knockout mice (110). Additionally, TFEB is a major regulator of lysosomal biogenesis and autophagy. Long-term feeding of HFD leads to a decrease in the expression of TFEB specifically in liver cells, resulting in impaired lipolysis metabolism in the liver and hepatic fatty degeneration. Overexpression of adenovirus TFEB restores the autophagy flow and improves liver fatty degeneration in similar animal models (111). However, Cao *et al* (112) discovered that in a mouse model of NAFLD and in *in vitro* cell culture systems, M2-type macrophages promote hepatic stellate cell (HSC) autophagy by secreting prostaglandin E2, which binds to the EP4 receptor on the HSC surface. This process subsequently exacerbates HSC activation, extracellular matrix deposition, and liver fibrosis, thereby promoting disease progression (112). In the white adipose tissue of mice fed a HFD, the levels of Rubicon, a negative regulator of autophagy, were decreased, accompanied by increased autophagic flux. Adipocyte-specific ATG7-knockout mice exhibited reduced serum FFA levels and alleviated HFD-induced lipotoxicity, hepatic inflammation, and fibrosis. These findings suggest that autophagy inhibition in white adipose tissue ameliorates liver pathology in NAFLD through adipose-liver crosstalk (113). In summary, autophagy plays an dual role in hepatic lipid metabolism, and autophagy dysfunction-induced lipid metabolism abnormalities may be a potential cause of NAFLD.

It is worth noting that the lack of autophagy in the liver can also lead to liver damage and increased inflammation. Research has found that Rubicon, a negative regulator of autophagosome-lysosome fusion that interacts with Beclin 1, is overexpressed in the liver tissues of mice fed with HFD, resulting in ER stress, cell apoptosis, and increased lipid accumulation in liver cells. At the same time, specific knockout of Rubicon shows a significant reduction in liver steatosis and damage (114). Moreover, further research has shown that autophagy can block the damage caused by lipopolysaccharide (LPS) to the liver of mice. Specifically, liver cell-specific autophagy knockout mice exhibit increased liver damage and mortality due to high-dose LPS (115), suggesting the role of autophagy in protecting against liver damage and inflammatory responses. Consistent with this, as autophagy decreases, IL-1β induces cytotoxicity and pro-inflammatory reactions in liver cells, leading to the occurrence of liver damage. Therefore, therapies that increase autophagy may be effective methods for treating liver diseases such as NAFLD (116). Collectively, during the progression of NAFLD, autophagy may initially facilitate lipid clearance at early stages, yet subsequently contribute to the amplification of cell death or inflammatory signaling. However, whether regulatory molecules such as Rubicon consistently assume the same functional role across distinct disease phases, from simple steatosis to steatohepatitis, remains to be further elucidated. Moreover, while most research has focused on the effects of autophagy deficiency or enhancement, relatively less attention has been paid to autophagic flux, selective autophagy, and the functional shifts of autophagy-related proteins within the pathological microenvironment. Future research should systematically dissect the dual-edged role of autophagy in the evolution of liver disease and its underlying regulatory networks, thereby providing a more precise theoretical foundation for the development of phase-adapted therapeutic strategies for liver disorders.

Atherosclerosis. Atherosclerosis is a progressive and complex disease characterized by excessive lipid accumulation in the arterial intima. Abnormal lipid metabolism, insulin resistance, inflammatory response, endothelial dysfunction, imbalance of adipocytokines, and activation of inflammasomes, among other mechanisms, may play a crucial role in the relationship between obesity and atherosclerosis (117). Among the various cell types involved in the formation of atherosclerotic plaques, autophagy is dysregulated in macrophages, vascular smooth muscle cells (VSMCs), and endothelial cells, which are of vital importance for the initiation and development of atherosclerosis. The changes in autophagy levels in these three types of cells are next examined (118).

Monocyte-derived macrophages play a crucial role throughout the entire pathological process of atherosclerosis, from its onset, progression, to eventual plaque rupture (119). Research has shown that the autophagy process of macrophages plays a critical protective role in atherosclerosis, and inhibiting macrophage autophagy can activate the mechanism of plaque instability and trigger necrotic reactions. However, inducing macrophage autophagy through mTORC1 can effectively stabilize atherosclerotic plaques (120). Consistent with this, in a mouse model of atherosclerotic plaque, it was found that macrophages had impaired autophagic function, with decreased ATG14 expression. Overexpressing ATG14 in macrophages enhanced the fusion of autophagosomes and lysosomes, promoted lipid degradation, and reduced oxidized low-density lipoprotein (oxLDL)-induced cell death and inflammatory responses (121). Additionally, Li *et al* (122) revealed in a mouse model of atherosclerosis that the level of dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1 (Dax1) in atherosclerotic plaques was elevated, and Dax1 inhibited autophagy by interacting with TFEB, leading to lipid accumulation in macrophages and inflammation. By reducing the level of Dax1 in mice using 2'-deoxycytidine, autophagy was enhanced, and the progression of atherosclerosis was inhibited (122). However, regulatory molecules

such as mTORC1, ATG14, and Dax1 may exert dynamic or even opposing functions at different stages of atherosclerosis. Future research should integrate temporally controlled models with cell-specific intervention strategies to systematically dissect the mechanistic roles of autophagy across distinct pathological phases of atherosclerosis. Such efforts will provide a more precise theoretical foundation for the development of stage-adapted therapeutic targets. Therefore, further exploration of the specific mechanisms regulating macrophage autophagy may yield promising therapeutic targets for treating atherosclerosis. Secondly, as the main component of the vascular wall, VSMCs play a key role in the development of atherosclerosis by converting from a contractile phenotype to a synthetic phenotype or a macrophage-like phenotype (123). Regular autophagic activity is associated with the survival and stability of SMCs, but excessive autophagy leads to SMC death and plaque instability. A previous study has shown that in the early stage of atherosclerosis, when SMCs are exposed to medium concentrations of oxLDL (10-40 μg/ml), autophagy is activated as a protective mechanism; while in the late stage of atherosclerosis, when exposed to high concentrations of oxLDL (≥60 μg/ml), the protective effect of autophagy weakens and instead exacerbates autophagy-induced cell death (124). Liu *et al* (125) found in a mouse model of atherosclerosis that Paeonol can induce autophagy in VSMCs by activating the PI3KC3/Beclin 1 signaling pathway, inhibit VSMC apoptosis, and alleviate the progression of atherosclerosis. However, although pharmacological interventions such as Paeonol have demonstrated protective effects under specific conditions, whether these effects remain consistent across different pathological stages and distinct cellular states requires systematic validation. Future research should further elucidate the spatiotemporally specific mechanisms governing the dynamic regulatory network of autophagy in SMCs, thereby providing a more precise theoretical foundation for stage-adapted therapeutic strategies in atherosclerosis. Finally, the flat cells located on the inner side of the vascular wall, vascular endothelial cells, have a key function in maintaining homeostasis. Vascular endothelial dysfunction is a key step in the formation of atherosclerosis (126). In mice models with excessive lipids, endothelial autophagy was revealed to play a vital role in limiting lipid accumulation in the vascular wall and maintaining lipid homeostasis. The absence of endothelial autophagy significantly increased the burden of atherosclerosis (127). Consistent with this, Ding *et al* (128) found that after oxLDL treatment, there was a decrease in v-Myb avian myeloblastosis viral oncogene homolog-like 1 expression in endothelial cells, leading to a reduction in pleckstrin homology domain containing, family M member 1 expression, inhibition of endothelial autophagy, and ultimately induction of endothelial cell apoptosis, promoting the formation of atherosclerotic plaques (128). Therefore, stimulating endothelial cell autophagy may be particularly beneficial for the treatment of atherosclerotic vascular diseases.

5. Therapies for autophagy

Lifestyle changes and exercise. Changes in lifestyle, such as calorie restriction, weight loss, and physical exercise, can reverse metabolic rigidity, meaning the reduced ability to adjust substrate oxidation based on available substrates, as well as obesity, and insulin resistance. Dietary restriction has been proven to be beneficial for weight gain caused by excessive nutrient intake and complications related to obesity (129,130). Gao *et al* (131) found that in obese and T2DM animal models (db/db mice and mice fed a HFD), moderate (40%) calorie restriction reversed β-cell dysfunction and insulin resistance in obese mice induced by diet, and restored glucose homeostasis, these changes being related to the upregulation of autophagy in β-cells (131). Moreover, in obesity-induced diabetic mouse models, it was found that modified forms of calorie restriction, namely intermittent fasting, could restore the autophagy flux in the pancreas and improve glucose tolerance by enhancing glucose-stimulated insulin secretion, β-cell survival, and pancreatic regeneration markers such as neurogenin 3 nuclear expression, but could not rescue β-cell death (132). In addition, Roux-en-Y gastric bypass (RYGB) surgery was demonstrated to rapidly reduce liver lipid toxicity in T2DM obese rats and improve insulin sensitivity. The mechanism is related to RYGB improving metabolic parameters, increasing plasma glucagon-like peptide-1 (GLP-1), activating autophagy, and reducing liver fat load (133). A clinical trial conducted by Guevara-Cruz *et al* (134) demonstrated that modifications in caloric intake, such as caloric restriction, or adjustments in meal timing, exemplified by intermittent fasting, play a significant role in stimulating both cellular autophagy and mitophagy, thereby facilitating the elimination of aged and dysfunctional mitochondria (134). Future research should systematically evaluate the safety profile of autophagy-based interventions and explore personalized dietary restriction strategies tailored to the specific metabolic phenotypes of patients.

It has long been recognized that exercise is a powerful physiological stimulus for various metabolic adaptations, exerting significant impacts on health and diseases. Exercise training promotes autophagy and improves maximal oxygen uptake and is considered a proper physiological stimulus for promoting metabolic adaptations beneficial to health (135). For example, Xiang *et al* (136) found that, compared with metformin, exercise alone was more effective in inhibiting the ubiquitin-proteasome system, increasing the level of autophagy, and alleviating skeletal muscle atrophy. This is mainly achieved by promoting the synthesis and degradation of autophagy through the AMPK/ULK1 pathway (136). This study indicates that exercise-induced autophagy plays a crucial role in the related complications of T2D. In addition, exercise is the first-line treatment and an important preventive measure for patients with NAFLD. In a non-alcoholic fatty liver mouse model with a HFD, it was found that 12-week swimming exercise prevented hepatic lipid accumulation and alleviated hepatocyte injury in HFD mice. This was mainly related to the fact that exercise significantly reduced the expression of the lipid metabolism gene fatty acid binding protein 1, restored lysosomal function (including lysosomal proteolysis and maintenance of lysosomal acidification), and increased autophagic flux (137). Consistent with this result, 15 weeks of moderate treadmill exercise in mice improved the histological phenotype of NAFLD, including hepatic steatosis, inflammation, and ballooning degeneration. It prevented HFD-induced hepatic fat deposition and liver injury. This was mainly related to the inhibition of abnormal lipid droplet expansion and the

enhancement of lysosomal clearance of lipid droplets during lipophagy (138). In addition, physical exercise is also considered a potential form of 'beneficial medicine' for treating atherosclerosis. Li *et al* (139) found that long-term swimming exercise could reduce weight gain in ApoE mice, improve arterial structural disorder, reduce the burden of atherosclerotic lesions, decrease the serum concentrations of total cholesterol, total triglycerides, soluble intercellular adhesion molecule-1, MMP-9, and IL-6, and increase the expression of autophagy markers LC3 and Beclin 1 (139). Moreover, regular exercise could enhance IL-1 signaling, stimulate endothelial cell autophagy, maintain the homeostasis of arterial endothelial cells in ApoE-deficient mice, and protect arteries from vascular diseases (140). Therefore, the benefits of exercise may be related to the autophagy mechanism, which is the basis for its positive effects on obesity-related metabolic diseases.

Pharmacological intervention. Given the crucial role of autophagy in the development of various human diseases, numerous studies have been conducted to develop drugs targeting autophagy. To date, the research on drugs targeting autophagy regulation has mainly focused on cancer, neurodegenerative diseases, and infectious diseases. Although no clinical trials using autophagy-targeting drugs for treating metabolic diseases have been carried out yet, the latest research indicates that existing or under-development drugs or compounds related to metabolic diseases may exert therapeutic effects by regulating the autophagy process. The roles of autophagy activators and inhibitors in obesity-related metabolic diseases are next summarized.

Autophagy activators. The activation of autophagy is mainly achieved by activating AMPK and/or inhibiting the PIK3CA/AKT/MTOR signaling pathway. AMPK, as the primary energy sensor in cells, responds to changes in the ATP-to-AMP ratio within cells. The activation of AMPK provides a powerful target for triggering autophagy (141). AICAR is considered one of the most commonly used pharmacological regulators of AMPK activity, and it can cause allosteric activation of AMPK (142). For mice with T2D induced by a HFD, AICAR treatment led to weight loss, reduction in abdominal fat volume and quality, and improvement in the pathological morphology of internal organs, indicating that AICAR has certain therapeutic potential in treating T2D (143). Additionally, it was found that the use of AICAR could prevent or reverse diabetic peripheral neuropathy in both T2D and T1D mouse models, which was related to increased AMPK phosphorylation and activation of mitochondrial autophagy (144). Secondly, metformin, as a first-line anti-diabetic drug, was shown to effectively alleviate glucose and lipid metabolism disorders, renal function damage in diabetic rats, oxidative stress in glomerular cells cultured under HG conditions, and enhanced autophagy levels, protecting the pathological process of diabetic nephropathy (145). Concurrently, You *et al* (146) also found that metformin, by activating the AMPK-mTOR pathway, induces autophagy and has a specific improvement effect on the development of atherosclerosis (146). In addition, thiazolidinedione drugs are widely used in clinical practice to improve insulin sensitivity. It was found that rosiglitazone could induce phosphorylation of AMPK and reduce phosphorylation of p70S6 kinase (p70S6K). Inhibition of AMPK impaired autophagy activation and exacerbated apoptosis induced by palmitate, suggesting that rosiglitazone-induced autophagy contributes to its protective function during palmitate treatment of β cells (147). Finally, resveratrol is a well-known polyphenolic compound with anti-obesity, antitumor, anti-diabetic, antioxidant, and anti-aging effects (148). In a mouse model of hepatic steatosis, resveratrol induced autophagy through the cAMP-PRKA-AMPK-SIRT1 signaling pathway, partially improving hepatic steatosis in mice (149). Moreover, Xu *et al* (150) found that resveratrol activates AMPK and JNK1, thereby inhibiting mTOR and its downstream effectors p70S6K1 and eukaryotic translation initiation factor 4E-binding protein 1, and disrupting the Beclin 1-Bcl-2 complex, inducing myocardial cell autophagy and reducing myocardial cell death to protect myocardial cells (150). Based on the aforementioned, it is considered that preclinical studies of autophagy activators are promising; however, further clinical research is still required to evaluate the efficacy and safety of these treatments.

The PIK3CA/AKT/mTOR signaling pathway is the most extensively studied autophagy-inhibiting pathway. Small molecule compounds that inhibit the AKT, mTOR, and PIK3CA complexes within this pathway can be used as potent autophagy inducers (151). There are two direct strategies for targeting mTOR activity. Firstly, rapamycin, as an mTOR inhibitor, modulates the activity of mTOR kinase through allosteric regulation and activates autophagy (152). For example, in the microglia and astrocytes of mice fed with HFDs, it was found that neuroinflammation increased, autophagy and brain-derived neurotrophic factor (BDNF) levels decreased, AMPK phosphorylation was inhibited, mTOR phosphorylation was induced, and mice exhibited depressive and anxiety-like behaviors. After treatment with the mTOR inhibitor rapamycin, autophagy and BDNF levels increased, and depressive and anxiety-like behaviors were also improved to a certain extent (153). Consistent with this, in the mouse model of diabetes nephropathy caused by obesity, it was found that the treatment with mTOR inhibitors improved the autophagy dysfunction of proximal renal tubular epithelial cells mediated by obesity and restored autophagy in the proximal renal tubules, improving the renal outcomes of obese patients (154). In addition to rapamycin, the mTOR inhibitor eptifibatide is expected to become a new therapeutic drug for NASH or diseases related to macrophage autophagy dysregulation. It was found that in LPS-induced macrophages, eptifibatide improved liver autophagy and NASH by inhibiting the ROS/p38/Nrf2 axis and the PI3K/AKT/mTOR pathway and enhancing macrophage autophagy, further inhibiting the progression of NAFLD (155). Secondly, small molecules such as Torin1/2, PP242, and AZD8055 that target the ATP-binding site of mTOR inhibit its kinase activity through ATP-competitive inhibition (156,157). However, this strategy is mainly applied in antitumor treatment, and the therapeutic prospects for obesity-related metabolic diseases need to be further explored in the future. Currently, AMPK pathway modulators, notably metformin, represent the strategy with the lowest risk and the most clearly defined path for clinical translation. Preclinical evidence has robustly supported the role of autophagy as a therapeutic target in metabolic diseases.

Future frameworks for translational medicine should prioritize the following directions: The development of tissue-specific or cell type-specific autophagy-modulating strategies to minimize systemic toxicity; in-depth investigations into the stage-dependent functions of autophagy to identify biomarkers capable of guiding therapeutic windows; and, upon establishing preclinical safety, the prioritization of clinical trials using metformin for specific metabolic complications, alongside early-phase translational studies of agents such as AICAR, in order to address critical gaps in human evidence.

Autophagy inhibitors. In addition to the therapeutic potential of autophagy inducers for treating metabolic abnormalities associated with obesity, inhibiting autophagy may also provide therapeutic benefits for obesity and its metabolic diseases. Strategies for inhibiting autophagy typically target the later stages of autophagy, including the inhibition of autophagosome formation (the initiation and maturation processes) and lysosomal degradation.

For the initiation of autophagy and the formation of autophagosomes, small molecules and natural products targeting the ULK1 complex and PI3KC3-C1 are two primary methods for inhibiting the initiation of autophagy, which leads to the blockage of autophagosome biogenesis. The ULK inhibitors MRT67307 and MRT68921 were selected from a series of closely related analogs generated during the initial TANK-binding kinase 1 screening process and are currently mainly used for antitumor treatment (158). Another early identified ULK inhibitor, SBI-0206965, also exhibits potent inhibition of AMPK or ULK1 signal transduction and cellular function (159). However, preclinical and clinical evidence regarding their application in metabolic diseases such as obesity and T2D remains largely absent, and their efficacy, specificity, and safety in the context of metabolic disorders are entirely unknown. Additionally, a pan-PI3K inhibitor, 3-MA, is widely used as an effective experimental tool to block the early stage of autophagy. Research has found that 3-MA can temporarily block the PI3K complex (class III) that promotes autophagy, while continuously inhibiting the PI3K complex (class I) of autophagy (160). These kinase inhibitors have great potential in combating obesity-related metabolic diseases. However, it should be particularly noted that because these kinase inhibitors typically have broad kinase activity inhibition, they may cause adverse effects and even produce effects opposite to those intended.

Autophagy is a one-way ticket for lysosomal degradation. Inhibiting lysosomal activity can significantly block autophagic degradation. Lysosomal cavity alkalizing agents such as chloroquine (CQ) and hydroxychloroquine (HCQ) exert their effects by damaging lysosomal function and inhibiting autophagy. Mauthe *et al* (161) discovered that CQ can induce severe disorder in the autophagic independence of the Golgi and endolysosomal systems, inhibit the interaction between autophagosomes and lysosomes, and mediate autophagy impairment (161). Additionally, batroxobin A1, as an autophagy inhibitor, was shown to block the vacuolar H-ATPase (V-ATPase) enzyme, which is responsible for the acidification of lysosomes and other intracellular organelles (162). For instance, Hirao *et al* (163) found that batroxobin blocked V-ATPase, inhibited gluconeogenic enzymes and mitochondrial electron transfer enzymes in the kidneys of T2D rats, reduced glucose levels in renal cytoplasm, and improved plasma glucose levels in patients with T2D (163). In conclusion, drugs targeting lysosomal function, such as CQ and HCQ, hold the greatest potential for rapid clinical translation due to their established clinical availability and preliminary evidence of metabolic benefits. However, their well-known systemic side effects necessitate rigorous monitoring. By contrast, upstream targets such as ULK1 offer greater mechanistic precision, yet their pleiotropic effects and the current absence of metabolic disease-specific data render the path to clinical application considerably more protracted. To establish a robust translational medicine framework, future research must prioritize: i) The development of tissue-specific delivery strategies; ii) validation in more physiologically relevant chronic disease models; and iii) the conduct of rigorous early-phase clinical trials to delineate the safety windows and preliminary efficacy of distinct target inhibitors in patients with metabolic disorders.

Finally, in constructing a therapeutic framework targeting autophagy for metabolic diseases, it is essential to recognize the heterogeneity of metabolic risk across human populations. A typical illustration of this is the 'obesity paradox,' wherein a higher body mass index (BMI) is sometimes associated with lower mortality in specific patient groups with established cardiovascular conditions such as heart failure or coronary artery disease (164). This phenomenon underscores that BMI or body weight classification alone is insufficient to accurately reflect underlying metabolic status, regional fat distribution (such as visceral vs. subcutaneous adipose tissue), systemic inflammatory tone, or the extent of organ-specific steatosis. Future therapeutic strategies must incorporate more refined stratification parameters, including insulin sensitivity, hepatic fat content, specific autophagic flux biomarkers, and cardiovascular functional status, to guide patient segmentation and individualized intervention.

6. Conclusion and prospects

Autophagy, a highly conserved intracellular degradation system, plays a central role in maintaining cellular metabolic homeostasis. The present review systematically examined the basic concepts, classification, molecular mechanisms of autophagy, the regulation of autophagy by nutritional factors, and its pivotal role in obesity-related metabolic diseases such as T2D, NAFLD, and atherosclerosis. Research indicates that autophagy exerts a dual regulatory effect on pancreatic β-cell function, hepatic lipid metabolism, inflammatory responses, and vascular homeostasis: Moderate activation helps clear damaged organelles and abnormal proteins, thereby maintaining normal cellular function, whereas either excessive or insufficient autophagy may exacerbate metabolic disorders and tissue damage. Under metabolic stress conditions such as obesity, autophagy function is often dysregulated, further leading to lipid accumulation, insulin resistance, and worsened inflammation. Currently, lifestyle interventions and pharmacological approaches have demonstrated the potential to improve metabolic abnormalities by modulating autophagy pathways, suggesting that targeting autophagy may emerge as a novel therapeutic strategy for metabolic diseases. However, despite

extensive attention on autophagy in the metabolic field, several key issues remain to be elucidated: First, the mechanisms of autophagy vary across different tissues, necessitating the use of cell-specific gene-editing models to deeply dissect its regulatory networks; second, how nutrients (such as amino acids, glucose, and lipids) precisely regulate upstream signaling pathways of autophagy requires further exploration; third, most autophagy modulators are still in the preclinical research stage, and their specificity, safety, and long-term efficacy need systematic validation. Developing tissue-specific autophagy intervention strategies will be an important future research direction.

In summary, this review systematically integrated the basic knowledge and cutting-edge progress of autophagy in the field of metabolism, clarified its potential as a novel target for the treatment of metabolic diseases, and elucidated the core challenges in current research at three levels: Tissue-specific mechanisms, precise nutritional regulation, and clinical translation bottlenecks. It provided a clear roadmap for researchers and clinical practitioners to shift from basic understanding to precise intervention, ultimately offering novel perspectives and potential intervention methods for the prevention and treatment of obesity and related metabolic diseases.

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Authors' contributions

CL and XQ conceived the review. CL designed the scope and structure of the review. XQ performed structured literature searches. PL, DL, QG and CY critically synthesized and interpreted findings. YT revised major sections of the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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