Review

Autophagy: A Major Regulatory Factor in Glucose Metabolism

Meiqing Liu [1,2,†], Xuling Luo [2,†], Haoliang Hu [3,*], and Linxi Chen [2,*]

[1] Central Laboratory of Yan'an Hospital Affiliated to Kunming Medical University, Key Laboratory of Tumor Immunological Prevention and Treatment of Yunnan Province, The Afiliated Yan'an Hospital of Kunming Medical University, Kunming 650051, China
[2] Institute of Pharmacy and Pharmacology, Hunan Provincial Key Laboratory of Tumor Microenvironment Responsive Medication Research, Hunan Province Cooperative Innovation Center for Molecular Target New Medication Study, Hengyang Medical School, University of South China, Hengyang 421001, China
[3] Changde Research Centre for Artificial Intelligence and Biomedicine, Zoology Key Laboratory of Hunan Higher Education, College of Life and Environmental Sciences, Hunan University of Arts and Science, Changde 415000, China
* Correspondence: huhl@huas.edu.cn (H.H.); 1995001765@usc.edu.cn (L.C.); Tel.: +86-18612235887 (H.H.); +86-16517369666 (L.C.)
† These authors contributed equally to this work.
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Abstract: Autophagy is a conserved degradative process which facilitates the degradation of excessive or damaged proteins and organelles in lysosomes. It plays a crucial role in maintaining cellular homeostasis by liberating glucose and other nutrients, like amino acids and fatty acids, to support cellular functions during stress conditions and starvation. Glucose, an important carbohydrate in the human body sustains cellular life. Recent studies have highlighted the role of autophagy in glucose metabolism. In this review, we summarize the role of autophagy in glycogen metabolism, glycolysis, and gluconeogenesis. We also explore the relationship between autophagy and factors involved in glucose metabolism, such as ATP and calcium. Additionally, we discuss the effects of autophagy on diseases associated with abnormal glucose metabolism, including diabetes and insulin resistance (IR). Furthermore, we will provide an overview of potential medications that can improve glucose metabolism by regulating autophagy. Thus, as the main regulator, autophagy is promising as a therapeutic target for addressing abnormal glucose metabolism-related diseases.

Keywords: autophagy; glycogen; glycolysis; gluconeogenesis; diabetes; potential medication

1. Introduction

Glucose metabolism is a fundamental process that plays a critical role in maintaining cellular homeostasis and energy metabolism [1,2]. Glucose can be gradually catabolized to release energy and produce intermediates that can enter other metabolic pathways via a series of enzymatic reactions. Thus, it serves as the major source of ATP, enabling cells to conduct various cellular processes, such as biosynthesis, active transport, and signaling. In addition, glucose metabolism provides the carbon backbone for synthesizing molecules that are critical for cells growth, maintenance, and proliferation, such as nucleotides, amino acids, and lipids [3]. Regulation of glucose metabolism is a complex process with several regulatory mechanisms to ensure metabolic homeostasis. Glycolysis is one of the central pathways of glucose metabolism, which converts glucose to pyruvate, generating ATP and other intermediates [2,4]. Signaling pathways, such as the insulin signaling pathway, respond to nutrient availability, control the availability of glucose transporters on the cell surface, and regulate the phosphorylation of key enzymes of glycolysis. Furthermore, heterogeneous and transcriptional regulation of enzymes related to glycolysis plays important roles in fine-tuning glucose metabolism.

Autophagy is a "self-eating" phenomenon that maintains cellular homeostasis [5,6]. It can keep apart cytoplasmic components in autophagosomes and deliver them to lysosomes for degradation [7,8]. Macroautophagy (referred to as autophagy), microautophagy, and chaperone-mediated autophagy are the three types of autophagy [9]. It has been reported that macroautophagy is a highly conserved and evolutionarily ancient catabolic process, which involves a vesicular structure with a double-layer membrane, named autophagosome. This vesicle engulfs cellular proteins and organelles and delivers them to lysosomes [9]. Autophagy encompasses

different stages [10], including initiation, autophagosome formation, autophagosome membrane expansion and elongation, autophagosome membrane closure, and lysosomal fusion, finally degrading or recycling intracellular products [11]. Autophagy is controlled by several signaling pathways and occurs at basal level and during cellular stress.

The role of autophagy in glucose metabolism has been highlighted in numerous studies. We provide a comprehensive overview of the specific roles of autophagy in regulating glucose metabolism, including glycolysis, gluconeogenesis, and glucose oxidation. Additionally, we delineate the relationship between autophagy and factors related to glucose metabolism, such as ATP and calcium. Furthermore, we discuss the involvement of autophagy in abnormal glucose metabolism, which causes diseases, particularly diabetes and IR. Understanding the diverse roles of autophagy in glucose metabolism is essential to unravel the underlying molecular mechanisms and identify potential therapeutic targets for metabolic disorders.

2. The Process of Autophagy

Several factors can induce autophagy, including starvation, hypoxia, infection, medications, exercise, reactive oxygen species (ROS) [12,13], and apelin [14–16]. Patricia et al. [17] reported that the induction of autophagy is controlled by two signaling pathways: mammalian or mechanistic target of rapamycin complex 1 (mTORC1) and AMP-activated protein kinase (AMPK). They assemble and activate Unc51-like kinase 1 (ULK1, known as ATG1) complex, which comprises ULK1, ATG13, ATG101, and the focal adhesion kinase (FAK) family kinase-interacting protein of 200kDa (FIP200, known as RB1CC1). Then, this complex activates the phosphatidylinositol 3-kinase (PI3K) complex, which induces the amalgamation of phosphatidylinositol 3-phosphate into the phagophore membrane and generates autophagosomes [18]. Autophagosome formation involves many genes, which are named autophagy-related genes (ATG).

Next, two conjugation reactions promote autophagosomes formation, both of which are catalyzed by ATG7. On the one hand, in the presence of autophagy-related16-like 1 (ATG16L1), ATG5 binds to ATG12. This process relies on ATG7 and ATG10. Then, the ATG5-ATG12 complex binds to ATG16L1 to expand the membrane of autophagosomes. On the other hand, ATG4B binds to ATG7 to form the ATG4B-ATG7 complex and induce the combination of phosphatidyl ethanolamine (PE) to LC3 (MAP1LC3) to create the autophagosome marker LC3-II (known as MAP1LC3B). The continuous assembling of these complexes and lipid delivery via the only multi-membrane-spanning ATG protein ATG9 allows the elongation of the autophagosome membrane to form the mature autophagosome [10]. Finally, autophagosomes integrate with lysosomes to degrade the contents. The macromolecular precursors can be used as fuels or recycled in the metabolic pathways. This part is summarized in Figure 1.

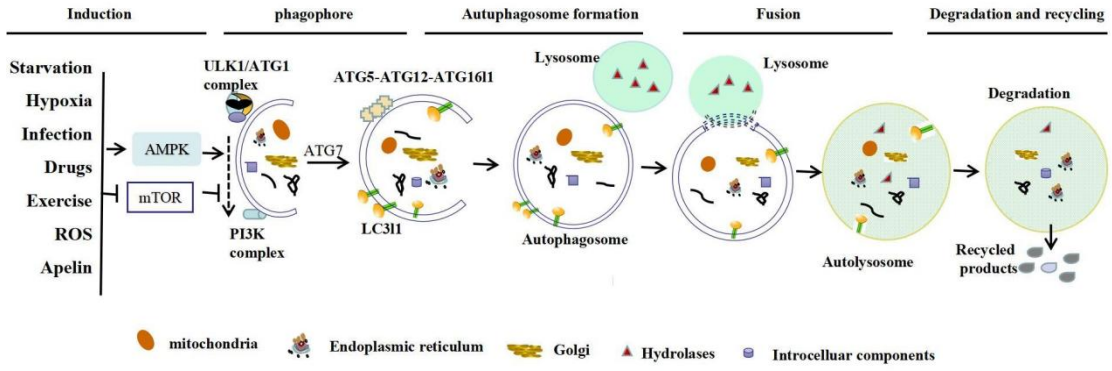

Figure 1. Autophagy involves a series of coordinated processes.

Autophagy induction activates AMPK and mTORC1, which subsequently induce the ULK1/ATG1 complex, triggering the PI3K complex formation and autophagosome generation. Subsequently, ATG7 facilitates conjugation reactions that support autophagosomes formation. Firstly, ATG5 conjugates with ATG12, and then the ATG5-ATG12 complex binds to ATG16L1, facilitating the expansion of the autophagosome membrane. Thereafter, the ATG4B-ATG7 complex forms and allows the conjugation of phosphatidylethanolamine (PE) to LC3, forming LC3-II. Finally, the autophagosome joins the lysosome, leading to the degradation of their contents. Macromolecular precursors are either recycled or utilized for cellular processes.

3. Autophagy Affects Glucose Metabolism by Modulating Key Enzymes Related to Glucose Metabolism

3.1. Autophagy and Glycogen Metabolism

Glycogen is a glucose polymer, including hepatic glycogen and muscle glycogen serves as the primary energy source in the body. Hepatic glycogen is present in liver. Hepatocytes are the hepatic parenchyma cells of liver that carry out most of the physiological tasks, including glycogen metabolism [19]. Hepatic glycogen is a major source of blood glucose in the body, and its fluctuations are influenced by the circadian cycle, and basal autophagy exhibits a rhythmic behavior accompanying the body's glucose fluctuations in the liver [19,20]. Unlike hepatic glycogen, muscle glycogen is source of energy but not for blood glucose in the body, since the shortage of glucose-6-phosphatase in the muscle. Hepatic glycogen plays a major role in hepatocytes of the postnatal rats, a significant breakdown of glycogen has been observed, which was accompanied by the spatial and functional distribution of autophagic vacuoles in glycogen-containing cells [21–23]. Initially, these vacuoles are small and scarce, but become larger and more abundant with the progression of glycogen breakdown. They are mainly located at the borders of cytoplasmic glycogen stores [5,24–28]. The molecular structures of liver glycogen in newborn rats are different from those in adult animals. In the fetal and newborn rats, liver glycogen shows the Cotton effect, whereas adult rat liver glycogen does not show the Cotton effect in optical rotatory dispersion (ORD) and circular dichroism (CD) absorption spectra. The Cotton effect of newborn rat liver disappears 3 days after birth [29]. Besides, the branching degree of the two glycogens is also different since adult liver glycogen is slightly greater than fetal and neonatal glycogen [29]. This difference may cause by glycogen-specific autophagy named glycophagy [30], and related to PI3K since PI3K is highly activated during glycophagy [31,32]. Increased autophagic activity was observed in various conditions of accelerated glycogen mobilization, including phlorizin treatment, isolated embryonic hepatocytes, hypoxia, or nervous diseases [33–38]. Autophagy affects glycogen catabolism not only in animals but also in plants. For instance, in magnaporthe, autophagy induces glycogen catabolism to regulate asexual differentiation by activating MoATG8 and glycogen phosphorylase 1 (Gph1). MoATG8 is essential for autophagosome formation, which plays a crucial role in autophagic cells death during appressorium formation and infection-related morphogenesis in magnaporthe. Meanwhile, Gph1 mediates glycogen breakdown in the cytosol [39].

Glycogen is regulated by glycogen phosphorylase (PYG) and glycogen synthase (GS) [30,38]. PYG is the rate-limiting enzyme for glycogen degradation in the cytosol. There are three subtypes of PYG, including muscle-type glycogen phosphorylase (PYGM), brain-type glycogen phosphorylase (PYGB), and liver-type glycogen phosphorylase (PYGL) with distinct tissue distribution patterns and functions [40]. PYGM is mainly expressed in the skeletal muscle, which mobilizes and decomposes muscle glycogen to provide ATP for myocytes, especially in the conditional of exercise [40], which coincides with increasing autophagic and mitophagic flux [41]. PYGM responds strongly and cooperatively to AMP activation to control local energy needs [42]. PYGB is primarily expressed in the adult brain; however, recent studies indicated that it is also expressed in tumor, fetal, and heart tissues [40]. PYGL is predominantly expressed in the liver, which catalyzes hepatic glycogen breakdown to maintain the blood glucose level [40]. Glycogen can be transported to autophagosomes through a selective process named glycophagy via the interaction with starch-binding domain-containing protein 1(STBD1) and gamma-aminobutyric acid receptor-associated protein-like (GABARAP) family protein and degraded in lysosomes via alpha-acid glucosidase (GAA) [30]. PYGL knockdown activated the normal autophagy and glycophagy as indicated by increasing the expression of p62 GAA, GABARAPL1 and GABARAPL2 in glioblastoma [43]. However, in healthy zebrafish, high expression of PYGL activated autophagy, especially mitophagy, to mobilize hepatic glycogen to supply energy to confront the cold environment [44]. In summary, autophagy plays a pivotal role in regulating PYGM, PYGB, and PYGL effects during glycogen breaks down.

Glucose-1-phosphate is converted to UDP-glucose by UDP-glucose pyrophosphorylase. Glucose-1-P is primarily converted to glucose-6-P by phosphoglucomutase (PGM). However, PGM also catalyzes the reverse reaction, converting glucose-1-P to glucose-6-P. The dual role of PGM may not drive optimal glucose-1-P accumulation and glycogen synthesis. The conversion of GDP-glucose to glucose-1-P and GDP is catalyzed by metabolite control phosphorylase-1(mcp-1) in worms, which is also named GDP-D-glucose phosphorylase 1 (GDPGP1) in mammals [45]. Loss of mcp-1/GDPGP1 decreases steady-state glucose-1-P and glycogen levels. Notably, pyruvate and glucose-6-P levels remain unaffected. GS knockdown in cultured neurons led to similar effects [46,47]. Conversely, MCP-1/GDPGP1 overexpression yielded opposite results in hypoxic conditions [46,47]. Although numerous studies have demonstrated the correlation between MCP-1/GDPGP1 and GS, there is still a lack of direct evidence to confirm whether MCP-1/GDPGP1 affects glycogen synthesis through autophagy. GS plays an essential role in autophagy. GS overexpression alone significantly increased the expression of LC3-II, decreased SQSTM1/p62 levels, and increased the number of autophagosomes and autolysosomes in

neuronal cells [48]. In the D. melanogaster larva, GS knockdown effectively blocked CQ-induced autophagosome formation, implying that GS may be directly involved in autophagosome formation, as it localizes to these structures and interacts with Atg8 to form a complex [49].

As a highly evolutionarily conserved intracellular serine/threonine kinase, glycogen synthase kinase-3 (GSK3) can inhibit GS via phosphorylation, thus modulating glucose metabolism [50,51]. Insulin inhibits GSK3, then activates GS and leads to glucose deposition as glycogen [52,53]. Similarly, treating type 2 diabetes (T2D) and/or obesity in animal models by GSK3β stimulated GS activity, insulin secretion, and glucose metabolism in the liver and skeletal muscle in the short and long terms [52,53]. It improved the sensitivity to insulin and finally ameliorated glucose homeostasis [53]. GSK3 has also been implicated in glucose metabolism through autophagy. For example, GSK-3β inhibited autophagy to promote cell survival in human prostate cancer cells [54]. In monocytes, LPS inhibited mTORC1, decreased GSK-3β phosphorylation, and finally activated GSK-3β [55]. Weikel et al. [56] found that GSK-3β knockdown can decrease the expression of protein kinase B (PKB, also known as Akt) but enhance AMPK function and activate the transcription factor fork head box protein O1 (FOXO1), which can induce autophagosome formation in human aortic endothelial cells (HAECs). Russi et al. [57] reported that GSK-3α/β inhibition upregulated the LC3-II/LC3-I ratio and downregulated p62 expression in epithelioid sarcoma cells. However, activated GSK-3β phosphorylated ULK1, a downstream target of mTORC1, induces autophagy in hippocampal neural stem cells [51,58]. These findings suggest that GSK-3 can function as an upstream regulator of autophagy in the context of glycogen metabolism.

Overall, autophagy is crucial in promoting glycogen metabolism by regulating glycogen degradation and energy balance and adapting to various metabolic states. Moreover, autophagy is involved in glycogenesis through interaction with GSK3 and GS, whereas it regulates glycogen degradation by modulating Gph1.

3.2. Autophagy and Glycolysis

Glycolysis is a process of breaking down the glucose into the pyruvate. Glycolysis occurs in the cytoplasm of all cells in the absence (anaerobic) or presence of oxygen (aerobic). In the anaerobic condition, the end product of pyruvate is lactate; however, under aerobic conditions, pyruvate can be further oxidized to produce acetyl CoA then enters the tricarboxylic acid cycle (TCA cycle) to produce CO_2 and H_2O through oxidization [59]. Autophagy promotes glycolysis in response to nutrient deprivation [60], and this effect may relate to enzymes that regulate glycolysis process. Lock et al. [61] reported that Atg5 knockout decreases glycolytic flux and glucose uptake in mouse embryonic fibroblasts (MEFs). Autophagy could also regulate glycolysis in dengue virus (DENV) infection. It increases the expression of hexokinase 2 (HK2), a rate-limiting enzyme in glycolysis, and upregulates the protein levels of glucose transporter 1 (GLUT1), thereby enhancing glucose uptake [62]. The glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) can convert glyceradehyde-3-phosphate to 1,3-bisphosphoglycerate [63]. After transfecting HeLa cells with GAPDH and staurosporine, an apoptosis initiator, GAPDH translocates to the nucleus, upregulates Atg12, and promotes autophagosome formation [64]. GAPDH protects HeLa cells against cells death, which is associated with increased glycolytic flux [64]. After transfection with siramesine, GAPDH translocates to the plasma membrane, decreases GLUT1 pools, and inhibits glucose uptake [65]. Rheb is a small GTPase and acts as a proximal key activator of mTORC1. In HEK293 cells, GAPDH affects the interaction between Rheb and mTOR. GAPDH prevents Rheb from binding to mTOR, inhibiting mTORC1 activity in low glucose conditions [66]. However, high glycolytic flux exhibited the opposite effect [66]. GAPDH silencing or blocking the interaction between Rheb and GAPDH desensitized mTORC1 signaling to changes in glucose levels [66].

Glycolysis also is known as the Warburg effect in tumor cells. Autophagy promotes glycolysis by upregulating its key enzymes at the transcriptional or translational levels in hepatocellular carcinoma cells. This affects glucose metabolism and cancer progression. Circ_0020123 and circRNA of Eps15 homology domain containing protein 2 (EHD2) accelerate glycolysis but inhibits autophagy in non-small cell lung cancer (NSCLC) cells, indicating an interaction between glycolysis and autophagy [67]. Activation of autophagy increases monocarboxylate transporter 1 (MCT1) expression, which enhances glycolysis and metastasis in hepatic cancer [68]. Lactate dehydrogenase A (LDHA), a rate-limiting enzyme of glycolysis, promotes lactate production. Li et al. [69] demonstrated that starvation induces autophagy and improves aerobic glycolysis by upregulating the expression of LDHA in bladder cancer cells. This process was reversed by autophagy inhibition. Wang et al. [70] demonstrated that cadmium (Cd) induces glycolysis by increasing the protein level of GLUT1, pyruvate kinase M2 (PKM2), LDHA, and HK2 in A549 and HELF cells and promotes glucose uptake and lactate release. Autophagy is involved in Cd-induced glycolysis given that blocking autophagy by 3MA and CQ downregulated glycolysis related proteins. ATG5 or ATG4B knockdown showed the same effect, while ATG4B overexpression

enhanced glycolysis. In summary, ATG5, ATG12, LC3II, and mTOR constitute the principal autophagy pathway involved in glycolysis by modulating enzymes, like GAPDH, HK2, PKM2, and LDHA (Figure 2).

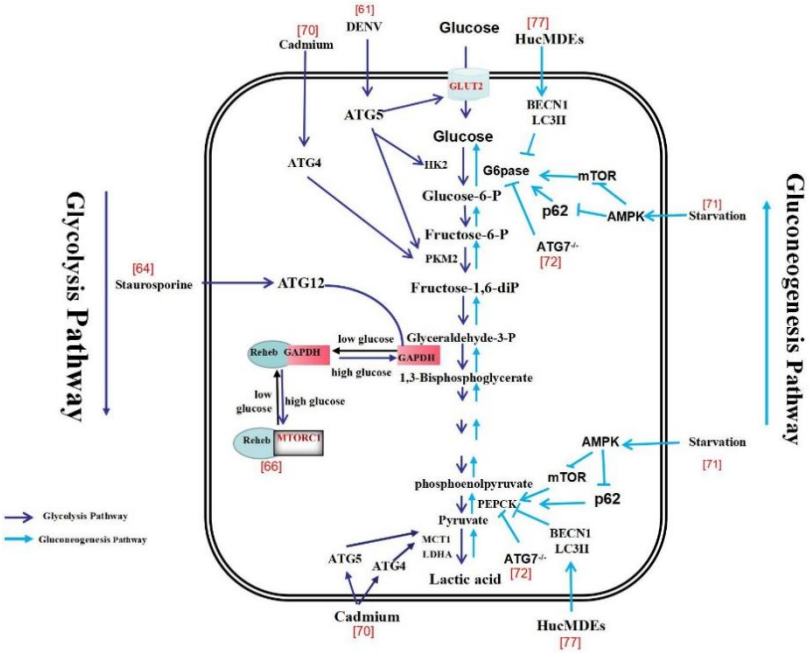

Figure 2. The involvement of autophagy in glycolysis and gluconeogenesis.

Starvation-induced autophagy decreases p62 level and activates LC3II and ATG5 to enhance PFKP expression. Cadmium induces ATG4 and ATG5 to increase GLUT1, HK2, PKM2, MCT1, and LDHA expression. Cadmium induces ATG4 and ATG5 to promote HK2, GLUT1, and PKM2 expression. DENV increases GLUT1 and HK2 through autophagy to regulate glycolysis. Staurosporine promotes GAPDH expression by upregulating ATG12. Under low-glucose conditions, GAPDH inhibits Rheb binding to mTOR, thereby inhibiting mTORC1 signaling. These pathways regulate glycolysis. Starvation induces autophagy by activating AMPK, downregulating mTOR and p62, and promoting G6pase and PEPCK expression to promote gluconeogenesis. Human umbilical cord mesenchymal stem cell-derived exosomes (HucMDEs) reduce gluconeogenesis by decreasing G6pase and PEPCK expression and increasing the expression of BECN1 and LC3II. ATG7 deficiency-mediated inhibition of autophagy impaired gluconeogenesis by decreasing G6Pase and PEPCK expression.

3.3. Autophagy and Gluconeogenesis

Gluconeogenesis is the process of new glucose molecule formation in the body. It primarily occurs in the liver and also occur in the kidney and small intestine. Autophagy can preserve energy and nutrients when nutrient supply is limited. It also helps maintain blood glucose levels by supporting gluconeogenesis.

In HepG2 cells, starvation induced autophagy by downregulating mTOR, p-mTOR, and p62 and activating AMPK. Meanwhile, the rate-limiting enzymes of gluconeogenesis, phosphoenolpyruvate carboxy kinase (PEPCK) and glucose-6-phosphatase (G6pase) were significantly upregulated [71]. Conversely, inhibition of autophagy due to ATG7 deficiency and absence of beclin1 impaired gluconeogenesis by decreasing PEPCK and G6Pase expression both in vitro and in vivo [72]. Fang et al. [73] reported that growth hormone (GH) activated autophagy, preserved triglyceride, enhanced gluconeogenesis, and finally prevented hypoglycemia in calorie-restricted mice. Autophagy participates in the maintenances of blood glucose levels by providing amino acids to convert [74]. In the holometabolous lepidopteran insect model, helicoverpa armigera, and cotton bollworm, autophagy provided substrates for gluconeogenesis. Silencing Atg8 blocked autophagy and decreased the production of gluconeogenesis substrates, such as glycerol and free amino acids (FAAs), finally decreasing glucose levels [75,76]. These findings demonstrate that autophagy provides amino acids to facilitate gluconeogenesis.

However, there is also a different perspective. Human umbilical cord mesenchymal stem cell-derived exosomes (HucMDEs) inhibited gluconeogenesis by decreasing the expression of gluconeogenic enzymes G6pase and PEPCK in L-O2 cells and T2DM rats. HucMDEs promoted autophagosome formation, evidenced by high expression of BECN1 and LC3II [77] (Figure 2).

3.4. Mitophagy Is Essential for Glucose Metabolism

Mitochondria is a metabolic organelle for glucose and fatty acids, involved in ATP sythesis [78]. Mitochondrial function is closely related to glucose level, glucose starvation and high glucose all could cause mitochondrial disorder, then lead to cellular metabolic dysfunction, such as abnormal glucose metabolism, as indicated by elevating ROS level, altering mitochondrial membrane potential (MMP) and chaotic ATP production [78–81]. Mitophagy is a selective degradation process by which cells remove and recycle aged or damaged mitochondria through autophagy to maintain mitochondrial and cellular homeostasis [81]. Advanced glycation end products (AGEs) and hyperglycemia-induced nucleus pulposus cells degeneration by aggravating the production of cellular ROS [82]. Excessive ROS causes genotoxicity and cellular damage [83], at this moment, mitophagy plays a protective role, removing the excessive ROS through the AMPK/mTOR/ULK1 pathway to rescue the cells [83].

The role of mitophagy in glycolysis is complex. Enhanced aerobic glycolysis often come with mitochondrial dysfunction, which causes low mitochondrial respiration causes increased ROS level [84]. Wang et al. reported that upregulating glycolysis with high expression of HK2 and 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) is accompanied by decreasing mitophagy [85]. However, Dai et al. with different standpoint, they reported that mitophagy was activated as evidenced by the upregulation of the mark genes pink1, parkin, LC3, Atg13, Atg12, and activation of glycolysis, indicated by the elevated HK and phosphofructokinase (pfk). In addition, during mitophagy activation, the glycogen content was increased, confirmed by increased glut1, GSK-3β, and glycogen synthase in the hepatopancreas [86].

Accumulation of β-amyloid (Aβ) in neurons of patients with Alzheimer's disease (AD) inhibits the activity of key enzymes in mitochondrial metabolic pathways, triggering mitochondrial dysfunction, which plays an important role in the onset and development of AD. Aberrant mitochondrial metabolism may hinder mitophagy, promote cellular metabolic dysfunction, such as abnormal glucose metabolism, and lead to neuronal death [87]. Mitophagy increases brain glucose metabolism by increasing brain ^{18}F-FDG uptake, oxygen consumption rate (OCR), ATP production, maximal respiration, spare respiratory capacity, and basal respiration in APP/PS1 cells [88].

In skeletal muscle, cold exposure impairs mitochondrial function, as indicated by the reduction in mitochondrial DNA content [89]. At this moment, mitophagy is activated to clear the damaged mitochondrial, thereby promote skeletal muscle glucose metabolism [89]. The activating of insulin IRS2/PI3K/AKT/GSK3β/GLUT4 pathway, leading to increased skeletal muscle glucose uptake, upregulated expression of the rate-limiting enzyme of glycogenolysis gene PYGL providing further evidence of reduced glycogen content [89]. Upregulated expression of the metabolism-related genes Hk1, Hk2, and PDK4 was observed following cold exposure [89]. During glycolysis process, glucose-6-phosphate dehydrogenase (G6PD) catalyzes the reaction of glucose 6-phosphate oxidating to be nicotinamide adenine dinucleotide phosphate (NADPH), G6PD knockdown activated mitophagy by PINK1/Parkin pathway [90].

4. Autophagy and Factors Involved in Glucose Metabolism

4.1. Autophagy and ATP

ATP serves as a vital signaling molecule involved in intercellular communication. It is the primary product of the TCA cycle. In A549 cells, decreased levels of intracellular ATP and changes in the ATP/AMP ratio regulate autophagy by activating AMPK and inhibiting p-mTOR [91,92]. Besides, autophagy regulates immunogenic cells death by promoting lysosomal ATP release [93]. Inhibition of autophagy hinders the release of ATP while inhibiting extracellular ATP-degrading enzymes elevates pericellular ATP levels in autophagy knockout tumors and recruits immune cells [94,95]. Extracellular ATP increases Ca^{2+} influx, which activates mTOR and leads to muscle hypertrophy [96]. Extrinsic ATP also promotes apoptosis by activating the purine receptor P2X7, and mTOR in MCA38 colon cancer cells [91,97]. In contrast, Jiang et al. [98] reported that extrinsic ATP stimulates the P2X7 receptor on the surface of tumor cells, but inhibits autophagy. Pannexin1, known as panx-1, is a type of membrane channel that is located in cellular membranes, and function as an ATP-permeable channel to allow ATP release from intracellular to extracellular [99]. Thus, elevated intracellular ATP causes the panx-1 channel activation. If the panx-1 is inhibited, low extracellular ATP levels and enhanced autophagy occur [91]. The above reports demonstrate that autophagy promotes endogenous ATP release, however, extrinsic ATP plays an inhibitory role.

4.2. Ca^{2+} Plays a Crucial Role in Regulating Glucose Metabolism through Autophagy

As a second messenger, calcium ions (Ca^{2+}) regulate several cellular processes, including glucose metabolism [91]. Ca^{2+} controls glucose metabolism by inhibiting glycogen synthase and activating glycogen phosphorylase, thereby regulating glycogenolysis and gluconeogenesis [59,100].

Plasma membrane calcium ATPases (PMCA) and Ca^{2+} release activated Ca^{2+} channels (CRACs) are two plasma membrane calcium channels that can maintain calcium homeostasis. PMCA actively pumps Ca^{2+} to the extracellular space, and CRACs often mediate the store-operated calcium channel entry [101]. Ca^{2+} release from the endoplasmic reticulum (ER) can activate CRACs. However, during high cytoplasmic concentration, Ca^{2+} is transported back into ER by the membrane pump sarcoplasmic/endoplasmic reticular calcium ATPase (SERCA) [101].

Ca^{2+} can activate or inactivate many proteins, such as molecular chaperones, enzymes, and transcriptional factors involved in autophagy [102]. Ca^{2+} is an important regulator of autophagy both in basal and induced levels [103]. It plays both stimulatory and inhibitory roles in autophagy [104]. For example, Yuan et al. [105] reported that autophagy is impaired in a Ca^{2+}-dependent manner. Factors increasing cytosolic Ca^{2+} levels, such as ATP, ionomycin, thapsigargin, vitamin D3, and its chemotherapeutic analog EB1089, can evoke autophagy, evidenced by LC3II translocation [106]. Ca^{2+} can be released from intracellular stores via calmodulin-dependent protein kinase kinase β (CaMKKβ)/AMPK/mTOR signaling pathway [102,107]. Ca^{2+} mediates glucose-stimulated insulin secretion (GSIS) to control glucose levels in β cells [108].

Glycophagy, an autophagic/lysosomal glycogen degradation pathway, is mediated by the transient upregulation of lysosomal acid α-glucosidase (GAA) [109]. Ca^{2+} enhances the glycogen hydrolyzing activity of α-glucosidase and accelerates glycogen degradation. This process is regulated by phorbol myristate acetate, which promotes Ca^{2+} entry into lysosomes [110].

High-voltage-activated (L-type) calcium channels and transient low-voltage-activated (T-type) calcium channels maintain cytosolic Ca^{2+} levels through different ages. These two calcium channels are often overexpressed in various diseases [111]. Studies have shown that blocking the L-type Ca^{2+} channel can induce mTOR-independent autophagy [112], and decrease fasting plasma glucose and glucose turnover in non-insulin-dependent diabetic patients, possibly by inhibiting gluconeogenesis [113]. Inhibition of L-type channel blocked glucose transport and diminished glycolytic intermediary molecules and glucose, leading to ATP depletion in several cell types [114,115]. Conversely, inhibition of L-type channel enhanced aerobic glycolysis, maintained ATP level in COLO 205 cells, and increased autophagic flux.

Mitochondrial pyruvate carrier (MPC) facilitates pyruvate transport into mitochondria. Pyruvate dehydrogenase (PDH) is a Ca^{2+}-dependent enzyme involved in the TCA cycle. Ca^{2+} binds to PDH phosphatase to promote PDH activity [116,117]. PDH phosphorylation changed the matrix Ca^{2+} level. Genetic deletion of MPC1 activated autophagy, attenuated mitochondrial pyruvate uptake, and decreased NADH production [118]. Ca^{2+} regulated the TCA cycle, lowered matrix Ca^{2+} levels, decreased PDH activity, and induced autophagy to compensate for substrate insufficiency (Figure 3).

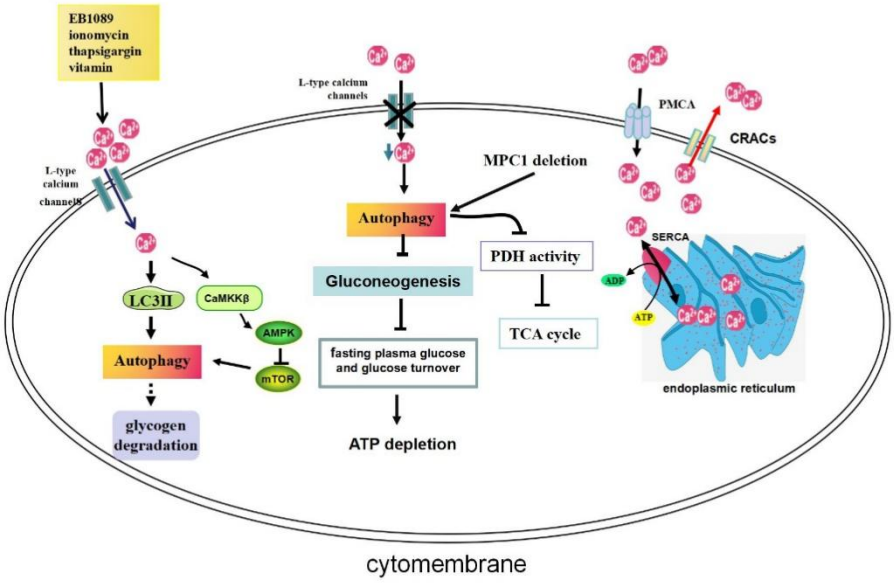

Figure 3. Ca^{2+} plays a crucial role in regulating glucose metabolism through autophagy.

PMCA actively pumps Ca^{2+} to the extracellular space, Ca^{2+} release from the endoplasmic reticulum through SERCA can activate CRACs, which mediate the Ca^{2+} transport to outside the cells. Calcium homeostasis is controlled by calcium channels. Factors increasing cytosolic Ca^{2+} levels, such as ATP, ionomycin, thapsigargin, vitamin D3, and its chemotherapeutic analog EB1089, can evoke autophagy, thereby affecting glycogen degradation. Low Ca^{2+} level and MCP1 deletion activate autophagy but block gluconeogenesis and TCA cycle then cause ATP depletion.

5. Autophagy Affects Diabetes and Insulin Resistance

Diabetes, especially type 2 diabetes, is a prevalent metabolic disorder characterized by hyperglycemia. It is caused by impaired insulin secretion from β cells and insulin resistance in peripheral tissues. Autophagy is controlled by insulin secretory granules in pancreatic β cells, which has been linked to increased incidences of T2D [119,120]. The relationship between impaired β cells and autophagy in T2D remains to be known. Rutter et al. [121] have reported that mTORC1 inhibition with rapamycin may lead to β cells death due to increased insulin release at low glucose concentrations. In autophagy $Becn1^{F121A}$-knockin mice, which are mice with autophagy hyperactivity, high-fat-diet challenge impaired glucose tolerance but improved insulin sensitivity compared to the control group [122]. Hyperactivation of autophagy enhanced insulin signaling but decreased insulin secretion through "vesicophagy" [122]. This process selectively degrades and sequesters insulin granules in β cells. Autophagy inhibitors transiently reversed reduced insulin secretion, glucose tolerance, and insulin storage. Intriguingly, autophagy plays a protective role in pancreatic β cells [108]. Insulin-deficient β cells exhibited increased LC3B-positive puncta levels. Inhibiting autophagy chemically or through shRNA enhanced β cells death, which was reversed by rapamycin [123]. Depletion of Atg7 by pancreatic intraductal AAV8-shAtg7 infusion in C57BL/6 mice decreased β cells mass, impaired glucose tolerance and insulin secretion, and enhanced apoptosis [124]. In vitro, rapamycin stimulated autophagy by increasing autophagosome formation and enhancing autophagosome-lysosome fusion in *Akita* β-cells. In vivo, treating diabetic *Akita* mice with rapamycin improved diabetes, increased pancreatic insulin content, and prevented β cells apoptosis [125]. These reports suggest that autophagy regulates β cells secretion in both harmful and beneficial manners. This dual effect may be affected by various factors, such as the specific pathological environment of β cells. Further studies are needed to fully understand the role of autophagy in type 2 diabetes.

IR is considered another major factor in T2D. What is the relationship between autophagy and IR? Some reports indicated that autophagy ameliorates IR. For example, Wang et al. [126] demonstrated that HFD induced IR and decreased autophagy-lysosomal proteins Beclin1, LC3II/I, ULK1, SQSTM1 expression, exercise significantly restored the impaired autophagy-lysosomal-related protein expressions, and improved glucose metabolism, and ultimately alleviating HFD-induced insulin resistance in mice skeletal muscle. Luan et al. [127] suggested that inhibition of autophagy by 3-methyladenine downregulated Beclin1 and LC3II/I and upregulated p62, thereby abolishing the inhibitory effect of the miR-138-5p inhibitor on IR in HepG2 cells and enhancing glucose uptake and glycogen synthesis. However, some studies found that autophagy inhibition was accompanied with IR. Mice with Atg3 and Atg16L1 ablation showed insulin resistance [128,129]. Autophagy was inhibited in the hepatic cells of T2D mice with insulin resistance [130]. Song et al. [131] indicated that inhibition of autophagy as evidenced by decreased LC3II/LC3I ratio and reduced expression of Atg5 and Atg7 improved IR in H9c2 cells. Skeletal muscle-specific deletion of Atg7 ameliorated diet-induced insulin resistance in mice [132]. Li et al. [133] suggested that palmitic acid (PA)-induced IR is accompanied by excessive activation of autophagy as evidenced by decreased expression of Atg12-Atg5, Atg16L1, and Atg3 in H9c2 cells during the first 24h and then decreased by 36 h. Thus, the effect of autophagy on insulin resistance remains inconclusive, potentially due to different pathways through which autophagy regulates insulin resistance in various experimental models and the varying roles of autophagy in different tissues.

6. Potential Drugs Regulating Autophagy to Treat Abnormal Glucose Metabolism

6.1. HucMDEs

Glucagon level is disproportionately increased in patients with T2DM and induces liver glycogen decomposition and hyperglycemia [77]. Recently, cell-based therapy has emerged as a promising treatment strategy for diabetes. HucMDEs are considered ideal choices for treating diabetes. Autophagy may play a crucial role in the therapeutic effects of HucMDEs in diabetes. For example, He et al. [77] reported that HucMDEs promote hepatic glycolysis by up-regulating the key glycolytic enzymes, GCK, PFK, and PK, while simultaneously downregulating the gluconeogenic enzymes G6pase and PEPCK. Furthermore, autophagy

potentially contributed to the beneficial effects of HucMDEs [77], evidenced by an increased abundance of autophagosomes and elevated levels of BECN1 and LC3II. Moreover, inhibition of autophagy significantly attenuated the effects of HucMDEs on glucose metabolism in rats with T2DM [77]. Thus, it can be inferred that HucMDEs exert their therapeutic effects on T2DM via autophagy (Figure 4).

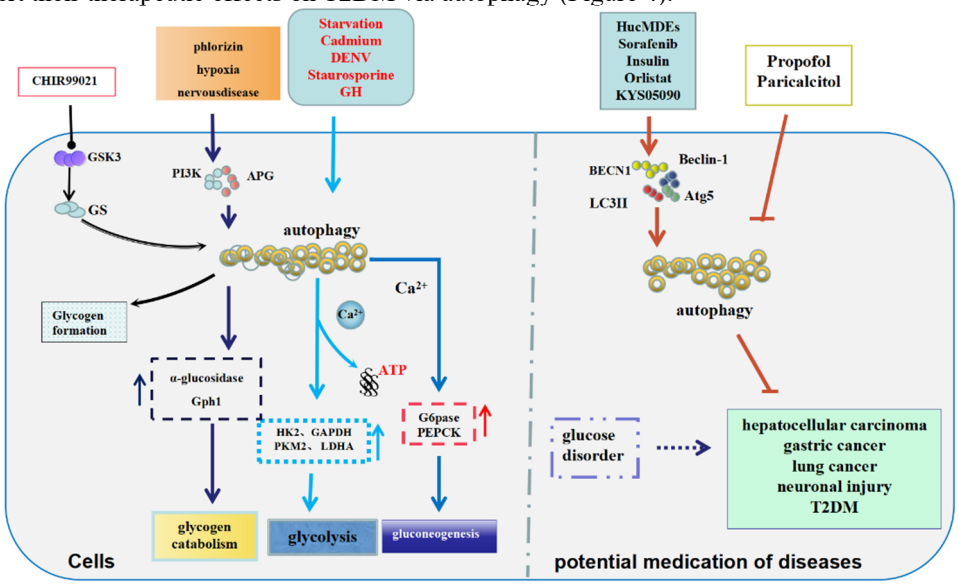

Figure 4. A schematic diagram depicting the role of autophagy in glucose metabolism and potential medication.

Autophagy is a conserved process that facilitates the degradation of damaged or excessive proteins and organelles in lysosomes. It plays a crucial role in maintaining cellular homeostasis during stress and starvation. Here, we summarized the role of autophagy in maintaining the homeostasis of glucose metabolism and discussed the effects of autophagy on diseases associated with abnormal glucose metabolism. Firstly, factors that induce autophagy often facilitate glucose metabolism through glycogenesis, glycogenolysis, glycolysis, and gluconeogenesis. Secondly, medications that improve abnormal glucose metabolism-associated diseases may activate or block autophagy.

6.2. Sorafenib

Sorafenib has garnered significant attention as the first FDA-approved medication for treating advanced hepatocellular carcinoma (HCC). However, its overall efficacy has been unsatisfactory. Enhanced glycolysis has been identified as a crucial resistance mechanism to sorafenib in HCC cells [134]. Studies suggested that sorafenib can promote autophagosome formation and increase the expression of Beclin-1, Atg5, and LC3II in vivo and in vitro [135]. Inhibiting autophagy significantly suppressed glycolysis and improved the sensitivity of HCC cells to sorafenib [136]. Furthermore, sorafenib induced autophagy to promote the deacetylase activity of HDAC6 by degrading p62, and subsequently promoting PKM2 activity [136]. Therefore, targeting autophagy-associated glycolysis may represent a potential strategy for improving sensitivity to sorafenib (Figure 4).

6.3. Orlistat

PGM1 plays a crucial role in regulating glucose metabolism by catalyzing the conversion of glucose-1-P to glucose-6-P reversibly. Cao et al. reported that high expression of PGM1 predicts shorter survival of patients with gastric cancer (GC) as analysed by Kaplan–Meier plotter database (kmplot.com/analysis) [137]. During glucose deprivation condition, PGM1 knockout significantly suppressed glycolysis, proliferation, and viability of cells, but enhanced the anti-cancer effects of orlistat [137]. Treatment with orlistat increased the average number of GFP-LC3 dots per cell and significantly up-regulated the expression levels of LC3-II [138]. Thus, considering the vital role of PGM1 in regulating glucose metabolism and autophagy, orlistat may exert its anti-cancer effect by modulating PGM1 and autophagy (Figure 4).

6.4. Propofol

Propofol (PPF) is an intravenous sedative-hypnotic agent and has been extensively utilized for general anesthesia and sedation. Neuronal injury often occurs due to glucose deprivation. Sun et al. [139] demonstrated

that PPF can antagonize oxygen-glucose deprivation and re-oxygenation (OGD/R)-induced neuronal injury by inhibiting autophagy through the Ca^{2+}/CaMKKβ/AMPK/mTOR pathway. Therefore, PPF can serve as a neuroprotective agent by inhibiting autophagy and subsequently regulating glucose levels (Figure 4).

6.5. Paricalcitol

Diabetic nephropathy (DN) is a serious microvascular complication of diabetes. The formation of advanced glycation end-products (AGE) is involved in the pathogenesis of DN. Li et al. [140] detected higher SQSTM1 expression, increased LC3-II level, and a higher abundance of autophagic vacuoles in the kidneys of vitamin D receptor (VDR) knockout diabetic mice. These changes were partly restored by paricalcitol, an activated vitamin D analog. Defective autophagy and decreased AMPK phosphorylation were also observed in high glucose-induced HK-2 cells, which was partly reversed by paricalcitol in a VDR-dependent manner [140]. Meanwhile, paricalcitol reversed the high glucose-induced decrease in Ca^{2+} concentration [140]. Thus, paricalcitol may inhibit AGE formation in diabetic nephropathy by regulating autophagy (Figure 4).

6.6. KYS05090

KYS05090 is a T-type calcium channel blocker. It induced autophagy in human lung adenocarcinoma A549 cells, which was inhibited by bafilomycin A, a potent autophagy inhibitor. Meanwhile, KYS05090 inhibited glucose uptake [141]. Thus, KYS05090 may treat lung cancer by inducing autophagy and inhibiting glucose uptake.

7. Conclusions and Prospective

Autophagy, as a cellular recycling mechanism, has been shown to regulate glucose metabolism. As presented in Figure 4, in this article, we have highlighted that autophagy regulates specific mechanisms in glucose metabolism, including glycogen metabolism, glycolysis, gluconeogenesis. Furthermore, the potential pharmacological agents that modulate autophagy and enzymes involved in glucose metabolism was also summarized. However, the relationship of these two biological processes is an intricate interplay, further studies are needed to determine the precise role of autophagy in glucose metabolism and ascertain whether it can be targeted to treat abnormal glucose metabolism.

Autophagy, as a promising target for treating abnormal glucose metabolism, is a novel target for future drugs development. Currently, some drugs have been developed to modulate autophagy, including the autophagy inducer rapalogs and the autophagy inhibitor 3-methyladenine. However, our knowledge of autophagy drugs remain limited, further studies are needed.

Future research should focus on elucidating the precise molecular mechanisms underlying autophagy's regulation in different stages of glucose metabolism. Additionally, targeting autophagy to investigate medication as potential treatments for glucose metabolism disorder source diseases like diabetes, insulin resistance and other metabolic diseases. Case studies and rigorous clinical trials must assess to take into account the safety and effectiveness of the medication, establish optimal treatment plans, and determine the appropriate dosages.

Exploring the relationship between autophagy and mitochondrial function is a crucial area for future research. Mitochondria is the primary site of glucose metabolism in cells, and defects in mitochondrial function have been linked to various metabolic disorders. Mitophagy is a selective autophagy has been shown to play a crucial role in maintaining mitochondrial homeostasis, confirming the underlying the relationship between mitophagy and glucose metabolism may provide new insights into the regulation of glucose metabolism and the development of metabolic disorders. Besides, understanding the role of other selective autophagy like lipophagy, reticulophagy, ribophagy, pexophagy on glucose metabolism could help in the study of drugs that regulate disorders of glucose metabolism leading to disease.

Lastly, studying the role of autophagy in different tissues and organs is crucial for a comprehensive understanding of its role in glucose metabolism. Although this article largely focused on the role of autophagy in the liver and muscles, its function in other tissues such as brain, heart, and adipose tissue needs to be further explored. The investigation of autophagy's role in these tissues may provide new insights into the regulation of glucose metabolism in these organs and its implications for various metabolic disorders.

In conclusion, this article shows that the exact role of autophagy in regulating normal and abnormal glucose metabolism is not well understood. Thus, future investigations on autophagy and glucose metabolism need to be strengthened to expand the current understanding and treatment of metabolic disorders. Such studies will pay the way for the development of innovative treatment strategies and novel drugs that can improve therapeutic outcomes for diseases associated with abnormal glucose metabolism.

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References

1. Poggiogalle, E.; Jamshed, H.; Peterson, C.M. Circadian regulation of glucose, lipid, and energy metabolism in humans. *Metabolism* **2018**, *84*, 11–27. https://doi.org/10.1016/j.metabol.2017.11.017.
2. Sajadimajd, S.; Bahrami, G.; Mohammadi, B.; Nouri, Z.; Farzaei, M.H.; Chen, J.T. Protective effect of the isolated oligosaccharide from Rosa canina in STZ-treated cells through modulation of the autophagy pathway. *J. Food Biochem.* **2020**, *44*, e13404. https://doi.org/10.1111/jfbc.13404.
3. Han, H.S.; Kang, G.; Kim, J.S.; Choi, B.H.; Koo, S.H. Regulation of glucose metabolism from a liver-centric perspective. *Exp. Mol. Med.* **2016**, *48*, e218. https://doi.org/10.1038/emm.2015.122.
4. Hernandez, F. Glycolysis and gluconeogenesis: A teaching view. *J. Biol. Chem.* **2021**, *296*, 100016. https://doi.org/10.1016/j.jbc.2020.100016.
5. Huang, F.; Wang, B.R.; Wang, Y.G. Role of autophagy in tumorigenesis, metastasis, targeted therapy and drug resistance of hepatocellular carcinoma. *World J. Gastroenterol.* **2018**, *24*, 4643–4651. https://doi.org/10.3748/wjg.v24.i41.4643.
6. Levine, B.; Klionsky, D.J. Development by self-digestion: Molecular mechanisms and biological functions of autophagy. *Dev. Cell* **2004**, *6*, 463–477. https://doi.org/10.1016/s1534-5807(04)00099-1.
7. McCarthy, M. Japanese cellular biologist wins Nobel prize for study of autophagy. *BMJ* **2016**, *355*, i5374. https://doi.org/10.1136/bmj.i5374.
8. Levine, B.; Klionsky, D. Autophagy wins the 2016 Nobel Prize in Physiology or Medicine: Breakthroughs in baker's yeast fuel advances in biomedical research. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 201–205. https://doi.org/10.1073/pnas.1619876114.
9. Mizushima, N.; Komatsu, M. Autophagy: Renovation of cells and tissues. *Cell* **2011**, *147*, 728–741. https://doi.org/10.1016/j.cell.2011.10.026.
10. Hurley, J.H.; Young, L.N. Mechanisms of Autophagy Initiation. *Annu. Rev. Biochem.* **2017**, *86*, 225–244. https://doi.org/10.1146/annurev-biochem-061516-044820.
11. Chu, C.T. Mechanisms of selective autophagy and mitophagy: Implications for neurodegenerative diseases. *Neurobiol. Dis.* **2019**, *122*, 23–34. https://doi.org/10.1016/j.nbd.2018.07.015.
12. Luo, Z.; Xu, X.; Sho, T.; Zhang, J.; Xu, W.; Yao, J.; Xu, J. ROS-induced autophagy regulates porcine trophectoderm cell apoptosis, proliferation, and differentiation. *Am. J. Physiol. Cell Physiol.* **2019**, *316*, C198–c209. https://doi.org/10.1152/ajpcell.00256.2018.
13. Qi, Z.; Chen, L. Endoplasmic Reticulum Stress and Autophagy. *Adv. Exp. Med. Biol.* **2019**, *362*, 11. https://doi.org/10.1007/978-981-15-0602-4_8.
14. Liu, M.; Li, H.; Zhou, Q.; Zhao, H.; Lv, D.; Cao, J.; Jiang, J.; Tang, M.; Wu, D.; Liu, J.; et al. ROS-Autophagy pathway mediates monocytes-human umbilical vein endothelial cells adhesion induced by apelin-13. *J. Cell. Physiol.* **2018**, *233*, 6839–6850. https://doi.org/10.1002/jcp.26554.
15. Xie, F.; Liu, W.; Feng, F.; Li, X.; He, L.; Lv, D.; Qin, X.; Li, L.; Li, L.; Chen, L. Apelin-13 promotes cardiomyocyte hypertrophy via PI3K-Akt-ERK1/2-p70S6K and PI3K-induced autophagy. *Acta Biochim. Biophys. Sin.* **2015**, *47*, 969–980. https://doi.org/10.1093/abbs/gmv111.
16. Zhe, C.; Jun, C.; Qun, Z.; Le-le, W.; Jia-Wei, C.; Xiang-Ning, D.; Jia-Long, Y.; Jian-Gang, C.; Xiao-Dan, X.; Lan-Fang, L.; et al. SEC62-dependent ER-phagy contributes to apelin-13/APJ-induced monocyte-vascular endothelial cell adhesion in atherosclerosis pathogenesis. *Acta Pharmacol. Sin.* **2025**, *46*, 1652–1663. https://doi.org/10.1038/s41401-024-01471-w.
17. Boya, P.; Codogno, P.; Rodriguez-Muela, N. Autophagy in stem cells: Repair, remodelling and metabolic reprogramming. *Development* **2018**, *145*, dev146506. https://doi.org/10.1242/dev.146506.
18. Butler, D.E.; Marlein, C.; Walker, H.F.; Frame, F.M.; Mann, V.M.; Simms, M.S.; Davies, B.R.; Collins, A.T.; Maitland, N.J. Inhibition of the PI3K/AKT/mTOR pathway activates autophagy and compensatory Ras/Raf/MEK/ERK signalling in prostate cancer. *Oncotarget* **2017**, *8*, 56698–56713. https://doi.org/10.18632/oncotarget.18082.

19. Qian, H.; Chao, X.; Williams, J.; Fulte, S.; Li, T.; Yang, L.; Ding, W.X. Autophagy in liver diseases: A review. *Mol. Asp. Med.* **2021**, *82*, 100973. https://doi.org/10.1016/j.mam.2021.100973.
20. Mikhail, R.; Anna, E.; Deborah, S.; Wenfang, X.; Eitan, O.; Samuel, B.; Petra, E.G.; Reid, R.T.; William, S.L.; Tamas, D.; et al. Diurnal Rhythms Spatially and Temporally Organize Autophagy. *Cell Rep.* **2019**, *26*, 1880-1892. https://doi.org/10.1016/j.celrep.2019.01.072.
21. Martinez-Lopez, N.; Singh, R. Autophagy and Lipid Droplets in the Liver. *Annu. Rev. Nutr.* **2015**, *35*, 215–237. https://doi.org/10.1146/annurev-nutr-071813-105336.
22. Filali-Mouncef, Y.; Hunter, C.; Roccio, F.; Zagkou, S.; Dupont, N.; Primard, C.; Proikas-Cezanne, T.; Reggiori, F. The ménage à trois of autophagy, lipid droplets and liver disease. *Autophagy* **2022**, *18*, 50–72. https://doi.org/10.1080/15548627.2021.1895658.
23. Kalamidas, S.; Kotoulas, O.; Kotoulas, A.; Maintas, D. The breakdown of glycogen in the lysosomes of newborn rat hepatocytes: The effects of glucose, cyclic 3′,5′-AMP and caffeine. *Histol. Histopathol.* **1994**, *9*, 691–698.
24. Kotoulas, O.B.; Ho, J.; Adachi, F.; Weigensberg, B.I.; Phillips, M.J. Fine structural aspects of the mobilization of hepatic glycogen. II. Inhibition of glycogen breakdown. *Am. J. Pathol.* **1971**, *63*, 23–36.
25. Kotoulas, O.B.; Phillips, M.J. Fine structural aspects of the mobilization of hepatic glycogen. I. Acceleration of glycogen breakdown. *Am. J. Pathol.* **1971**, *63*, 1–22.
26. Roach, P.J.; Depaoli-Roach, A.A.; Hurley, T.D.; Tagliabracci, V.S. Glycogen and its metabolism: Some new developments and old themes. *Biochem. J.* **2012**, *441*, 763–787. https://doi.org/10.1042/bj20111416.
27. Kalamidas, S.A.; Kotoulas, O.B. Studies on the breakdown of glycogen in the lysosomes: The effects of hydrocortisone. *Histol. Histopathol.* **2000**, *15*, 29–35. https://doi.org/10.14670/hh-15.29.
28. Kalamidas, S.A.; Kotoulas, O.B. The degradation of glycogen in the lysosomes of newborn rat hepatocytes: Glycogen-, maltose- and isomaltose-hydrolyzing acid alpha glucosidase activities in liver. *Histol. Histopathol.* **1999**, *14*, 23–30. https://doi.org/10.14670/hh-14.23.
29. Iwamasa, T.; Tsuru, T.; Hamada, T.; Takeuchi, T. Physicochemical and ultrastructural studies on glycogenosomes in newborn rat hepatocytes. *Pathol. Res. Pract.* **1980**, *167*, 363–373. https://doi.org/10.1016/s0344-0338(80)80065-3.
30. Zhao, H.; Tang, M.; Liu, M.; Chen, L. Glycophagy: An emerging target in pathology. *Clin. Chim. Acta* **2018**, *484*, 298–303. https://doi.org/10.1016/j.cca.2018.06.014.
31. Dong, J.; Guo, C.; Yang, Z.; Wu, Y.; Zhang, C. Follicle-Stimulating Hormone Alleviates Ovarian Aging by Modulating Mitophagy- and Glycophagy-Based Energy Metabolism in Hens. *Cells* **2022**, *11*, 3270. https://doi.org/10.3390/cells11203270.
32. Qiu, F.; Yuan, Y.; Luo, W.; Gong, Y.; Zhang, Z.; Liu, Z.M.; Gao, L. Asiatic acid alleviates ischemic myocardial injury in mice by modulating mitophagy- and glycophagy-based energy metabolism. *Acta Pharmacol. Sin.* **2021**, *43*, 1395–1407. https://doi.org/10.1038/s41401-021-00763-9.
33. Kalamidas, S.A.; Kotoulas, O.B. Glycogen autophagy in newborn rat hepatocytes. *Histol. Histopathol.* **2000**, *15*, 1011–1018. https://doi.org/10.14670/hh-15.1011.
34. David, H.; Reinke, P.; Bimmler, M. Postnatal development of hepatocytes following oxygen deficiency in utero. *Exp. Pathol.* **1986**, *30*, 247–256. https://doi.org/10.1016/s0232-1513(86)80084-6.
35. Devos, P.; Hers, H. Random, presumably hydrolytic, and lysosomal glycogenolysis in the livers of rats treated with phlorizin and of newborn rats. *Biochem. J.* **1980**, *192*, 177–181. https://doi.org/10.1042/bj1920177.
36. Kovács, A.L.; Eldib, A.; Telbisz, A. Autophagy in hepatocytes and erythropoietic cells isolated from the twenty-one day old rat embryo. *Acta Biol. Hung.* **2001**, *52*, 417–433. https://doi.org/10.1556/ABiol.52.2001.4.7.
37. Ohshita, T. Suppression of autophagy by ethionine administration in male rat liver in vivo. *Toxicology* **2000**, *147*, 51–57. https://doi.org/10.1016/s0300-483x(00)00180-3.
38. Lin, Q.; Shi, Y.; Liu, Z.; Mehrpour, M.; Hamaï, A.; Gong, C. Non-coding RNAs as new autophagy regulators in cancer progression. *Biochim. Biophys. Acta. Mol. Basis Dis.* **2022**, *1868*, 166293. https://doi.org/10.1016/j.bbadis.2021.166293.
39. Deng, Y.Z.; Ramos-Pamplona, M.; Naqvi, N.I. Autophagy-assisted glycogen catabolism regulates asexual differentiation in Magnaporthe oryzae. *Autophagy* **2009**, *5*, 33–43. https://doi.org/10.4161/auto.5.1.7175.
40. Yang, C.; Wang, H.; Shao, M.; Chu, F.; He, Y.; Chen, X.; Fan, J.; Chen, J.; Cai, Q.; Wu, C. Brain-Type Glycogen Phosphorylase (PYGB) in the Pathologies of Diseases: A Systematic Review. *Cells* **2024**, *13*, 289. https://doi.org/10.3390/cells13030289.
41. Franco-Romero, A.; Sandri, M.; Schiaffino, S. Autophagy in Skeletal Muscle. *Cold Spring Harb. Perspect. Biol.* **2024**, a041565. https://doi.org/10.1101/cshperspect.a041565.
42. Müller, M.S.; Pedersen, S.E.; Walls, A.B.; Waagepetersen, H.S.; Bak, L.K. Isoform-selective regulation of glycogen phosphorylase by energy deprivation and phosphorylation in astrocytes. *Glia* **2015**, *63*, 154–162. https://doi.org/10.1002/glia.22741.
43. Zois, C.E.; Hendriks, A.M.; Haider, S.; Pires, E.; Bridges, E.; Kalamida, D.; Voukantsis, D.; Lagerholm, B.C.; Fehrmann, R.S.N.; den Dunnen, W.F.A.; et al. Liver glycogen phosphorylase is upregulated in glioblastoma and provides a metabolic vulnerability to high dose radiation. *Cell Death Dis.* **2022**, *13*, 573. https://doi.org/10.1038/s41419-022-05005-2.
44. Chen, H.; Zhao, F.; Chen, K.; Guo, Y.; Liang, Y.; Zhao, H.; Chen, S. Exposure of zebrafish to a cold environment triggered cellular autophagy in zebrafish liver. *J. Fish. Dis.* **2022**, *45*, 991–1000. https://doi.org/10.1111/jfd.13620.

45. Schulz, A.; Sekine, Y.; Oyeyemi, M.J.; Abrams, A.J.; Basavaraju, M.; Han, S.M.; Groth, M.; Morrison, H.; Strittmatter, S.M.; Hammarlund, M. The stress-responsive gene GDPGP1/mcp-1 regulates neuronal glycogen metabolism and survival. *J. Cell Biol.* **2020**, *219*, e201807127. https://doi.org/10.1083/jcb.201807127.
46. Onkar, A.; Sheshadri, D.; Ganesh, S. Glycogen: The missing link in neuronal autophagy? *Autophagy* **2020**, *16*, 2102–2104. https://doi.org/10.1080/15548627.2020.1802090.
47. Adler, L.; Gomez, T.; Clarke, S.; Linster, C. A novel GDP-D-glucose phosphorylase involved in quality control of the nucleoside diphosphate sugar pool in Caenorhabditis elegans and mammals. *J. Biol. Chem.* **2011**, *286*, 21511–21523. https://doi.org/10.1074/jbc.M111.238774.
48. Li, I.H.; Ma, K.H.; Weng, S.J.; Huang, S.S.; Liang, C.M.; Huang, Y.S. Autophagy activation is involved in 3,4-methylenedioxymethamphetamine ('ecstasy')—induced neurotoxicity in cultured cortical neurons. *PLoS ONE* **2014**, *9*, e116565. https://doi.org/10.1371/journal.pone.0116565.
49. Zirin, J.; Nieuwenhuis, J.; Perrimon, N. Role of autophagy in glycogen breakdown and its relevance to chloroquine myopathy. *PLoS Biol.* **2013**, *11*, e1001708. https://doi.org/10.1371/journal.pbio.1001708.
50. Embi, N.; Rylatt, D.B.; Cohen, P. Glycogen synthase kinase-3 from rabbit skeletal muscle. Separation from cyclic-AMP-dependent protein kinase and phosphorylase kinase. *Eur. J. Biochem.* **1980**, *107*, 519–527.
51. Pan, H.Y.; Valapala, M. Regulation of Autophagy by the Glycogen Synthase Kinase-3 (GSK-3) Signaling Pathway. *Int. J. Mol. Sci.* **2022**, *23*, 1709. https://doi.org/10.3390/ijms23031709.
52. Cline, G.W.; Johnson, K.; Regittnig, W.; Perret, P.; Tozzo, E.; Xiao, L.; Damico, C.; Shulman, G.I. Effects of a novel glycogen synthase kinase-3 inhibitor on insulin-stimulated glucose metabolism in Zucker diabetic fatty (fa/fa) rats. *Diabetes* **2002**, *51*, 2903–2910. https://doi.org/10.2337/diabetes.51.10.2903.
53. Patel, S.; Doble, B.W.; MacAulay, K.; Sinclair, E.M.; Drucker, D.J.; Woodgett, J.R. Tissue-specific role of glycogen synthase kinase 3beta in glucose homeostasis and insulin action. *Mol. Cell Biol.* **2008**, *28*, 6314–6328. https://doi.org/10.1128/mcb.00763-08.
54. Yang, J.; Takahashi, Y.; Cheng, E.; Liu, J.; Terranova, P.F.; Zhao, B.; Thrasher, J.B.; Wang, H.G.; Li, B. GSK-3beta promotes cell survival by modulating Bif-1-dependent autophagy and cell death. *J. Cell Sci.* **2010**, *123*, 861–870. https://doi.org/10.1242/jcs.060475.
55. Wang, H.; Brown, J.; Gu, Z.; Garcia, C.A.; Liang, R.; Alard, P.; Beurel, E.; Jope, R.S.; Greenway, T.; Martin, M. Convergence of the mammalian target of rapamycin complex 1- and glycogen synthase kinase 3-β-signaling pathways regulates the innate inflammatory response. *J. Immunol.* **2011**, *186*, 5217–5226. https://doi.org/10.4049/jimmunol.1002513.
56. Weikel, K.A.; Cacicedo, J.M.; Ruderman, N.B.; Ido, Y. Knockdown of GSK3β increases basal autophagy and AMPK signalling in nutrient-laden human aortic endothelial cells. *Biosci. Rep.* **2016**, *36*, e00382. https://doi.org/10.1042/bsr20160174.
57. Russi, S.; Sgambato, A.; Bochicchio, A.M.; Zoppoli, P.; Aieta, M.; Capobianco, A.M.L.; Ruggieri, V.; Zifarone, E.; Falco, G.; Laurino, S. CHIR99021, trough GSK-3β Targeting, Reduces Epithelioid Sarcoma Cell Proliferation by Activating Mitotic Catastrophe and Autophagy. *Int. J. Mol. Sci.* **2021**, *22*, 11147. https://doi.org/10.3390/ijms222011147.
58. Ryu, H.Y.; Kim, L.E.; Jeong, H.; Yeo, B.K.; Lee, J.W.; Nam, H.; Ha, S.; An, H.K.; Park, H.; Jung, S.; et al. GSK3B induces autophagy by phosphorylating ULK1. *Exp. Mol. Med.* **2021**, *53*, 369–383. https://doi.org/10.1038/s12276-021-00570-6.
59. Akram, M. Mini-review on glycolysis and cancer. *J. Cancer Educ.* **2013**, *28*, 454–457. https://doi.org/10.1007/s13187-013-0486-9.
60. Keenan, M.M.; Chi, J.T. Alternative fuels for cancer cells. *Cancer J.* **2015**, *21*, 49–55. https://doi.org/10.1097/PPO.0000000000000104.
61. Lock, R.; Roy, S.; Kenific, C.M.; Su, J.S.; Salas, E.; Ronen, S.M.; Debnath, J. Autophagy facilitates glycolysis during Ras-mediated oncogenic transformation. *Mol. Biol. Cell* **2011**, *22*, 165–178. https://doi.org/10.1091/mbc.E10-06-0500.
62. Lee, Y.R.; Wu, S.Y.; Chen, R.Y.; Lin, Y.S.; Yeh, T.M.; Liu, H.S. Regulation of autophagy, glucose uptake, and glycolysis under dengue virus infection. *Kaohsiung J. Med. Sci.* **2020**, *36*, 911–919. https://doi.org/10.1002/kjm2.12271.
63. Dodson, M.; Darley-Usmar, V.; Zhang, J. Cellular metabolic and autophagic pathways: Traffic control by redox signaling. *Free Radic. Biol. Med.* **2013**, *63*, 207–221. https://doi.org/10.1016/j.freeradbiomed.2013.05.014.
64. Colell, A.; Ricci, J.E.; Tait, S.; Milasta, S.; Maurer, U.; Bouchier-Hayes, L.; Fitzgerald, P.; Guio-Carrion, A.; Waterhouse, N.J.; Li, C.W.; et al. GAPDH and autophagy preserve survival after apoptotic cytochrome c release in the absence of caspase activation. *Cell* **2007**, *129*, 983–997. https://doi.org/10.1016/j.cell.2007.03.045.
65. Craven, R.J.; Frazier, H.N.; Thibault, O. Dependence of glucose transport on autophagy and GAPDH activity. *Brain Res.* **2022**, *1776*, 147747. https://doi.org/10.1016/j.brainres.2021.147747.
66. Lee, M.N.; Ha, S.H.; Kim, J.; Koh, A.; Lee, C.S.; Kim, J.H.; Jeon, H.; Kim, D.H.; Suh, P.G.; Ryu, S.H. Glycolytic flux signals to mTOR through glyceraldehyde-3-phosphate dehydrogenase-mediated regulation of Rheb. *Mol. Cell Biol.* **2009**, *29*, 3991–4001. https://doi.org/10.1128/mcb.00165-09.
67. Yang, X.P.; Zheng, Y.Z.; Tan, J.; Tian, R.J.; Shen, P.; Cai, W.J.; Liao, H.Y. Circ_0020123 regulates autophagy, glycolysis, and malignancy by upregulating IRF4 through eliminating miR-193a-3p-mediated suppression of IRF4 in non-small cell lung cancer. *Neoplasma* **2022**, *69*, 392–403. https://doi.org/10.4149/neo_2022_211013N1449.

68. Fan, Q.; Yang, L.; Zhang, X.; Ma, Y.; Li, Y.; Dong, L.; Zong, Z.; Hua, X.; Su, D.; Li, H.; et al. Autophagy promotes metastasis and glycolysis by upregulating MCT1 expression and Wnt/β-catenin signaling pathway activation in hepatocellular carcinoma cells. *J. Exp. Clin. Cancer Res. CR* **2018**, *37*, 9. https://doi.org/10.1186/s13046-018-0673-y.
69. Li, T.; Tong, H.; Yin, H.; Luo, Y.; Zhu, J.; Qin, Z.; Yin, S.; He, W. Starvation induced autophagy promotes the progression of bladder cancer by LDHA mediated metabolic reprogramming. *Cancer Cell Int.* **2021**, *21*, 597. https://doi.org/10.1186/s12935-021-02303-1.
70. Wang, X.; Li, Z.; Gao, Z.; Li, Q.; Jiang, L.; Geng, C.; Yao, X.; Shi, X.; Liu, Y.; Cao, J. Cadmium induces cell growth in A549 and HELF cells via autophagy-dependent glycolysis. *Toxicol. Vitr.* **2020**, *66*, 104834. https://doi.org/10.1016/j.tiv.2020.104834.
71. Jeon, J.Y.; Lee, H.; Park, J.; Lee, M.; Park, S.W.; Kim, J.S.; Lee, M.; Cho, B.; Kim, K.; Choi, A.M.; et al. The regulation of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase by autophagy in low-glycolytic hepatocellular carcinoma cells. *Biochem. Biophys. Res. Commun.* **2015**, *463*, 440–446. https://doi.org/10.1016/j.bbrc.2015.05.103.
72. Wang, H.J.; Park, J.Y.; Kwon, O.; Choe, E.Y.; Kim, C.H.; Hur, K.Y.; Lee, M.S.; Yun, M.; Cha, B.S.; Kim, Y.B.; et al. Chronic HMGCR/HMG-CoA reductase inhibitor treatment contributes to dysglycemia by upregulating hepatic gluconeogenesis through autophagy induction. *Autophagy* **2015**, *11*, 2089–2101. https://doi.org/10.1080/15548627.2015.1091139.
73. Fang, F.; Shi, X.; Brown, M.S.; Goldstein, J.L.; Liang, G. Growth hormone acts on liver to stimulate autophagy, support glucose production, and preserve blood glucose in chronically starved mice. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 7449–7454. https://doi.org/10.1073/pnas.1901867116.
74. Ezaki, J.; Matsumoto, N.; Takeda-Ezaki, M.; Komatsu, M.; Takahashi, K.; Hiraoka, Y.; Taka, H.; Fujimura, T.; Takehana, K.; Yoshida, M.; et al. Liver autophagy contributes to the maintenance of blood glucose and amino acid levels. *Autophagy* **2011**, *7*, 727–736. https://doi.org/10.4161/auto.7.7.15371.
75. Wang, X.P.; Huang, Z.; Li, Y.L.; Jin, K.Y.; Dong, D.J.; Wang, J.X.; Zhao, X.F. Krüppel-like factor 15 integrated autophagy and gluconeogenesis to maintain glucose homeostasis under 20-hydroxyecdysone regulation. *PLoS Genet.* **2022**, *18*, e1010229. https://doi.org/10.1371/journal.pgen.1010229.
76. Yang, Y.; Zhao, C.; Yang, P.; Wang, X.; Wang, L.; Chen, A. Autophagy in cardiac metabolic control: Novel mechanisms for cardiovascular disorders. *Cell Biol. Int.* **2016**, *40*, 944–954. https://doi.org/10.1002/cbin.10626.
77. Stephenson, M.C.; Leverton, E.; Khoo, E.Y.; Poucher, S.M.; Johansson, L.; Lockton, J.A.; Eriksson, J.W.; Mansell, P.; Morris, P.G.; MacDonald, I.A. Variability in fasting lipid and glycogen contents in hepatic and skeletal muscle tissue in subjects with and without type 2 diabetes: A 1H and 13C MRS study. *NMR Biomed.* **2013**, *26*, 1518–1526. https://doi.org/10.1002/nbm.2985.
78. Du, Q.; Wu, X.; Ma, K.; Liu, W.; Liu, P.; Hayashi, T.; Mizuno, K.; Hattori, S.; Fujisaki, H.; Ikejima, T. Silibinin alleviates ferroptosis of rat islet β cell INS-1 induced by the treatment with palmitic acid and high glucose through enhancing PINK1/parkin-mediated mitophagy. *Arch. Biochem. Biophys.* **2023**, *743*, 109644. https://doi.org/10.1016/j.abb.2023.109644.
79. Lei, J.; Alexander, A.S.; Pamela, S.; Chendong, Y.; Seth, J.P.; Qiong, A.W.; Lance, S.T.; Nicholas, D.A.; Michael, T.M.; Beth, P.; et al. Reductive carboxylation supports redox homeostasis during anchorage-independent growth. *Nature* **2016**, *532*, 255–258. https://doi.org/10.1038/nature17393.
80. Xiong, Z.; Yang, L.; Zhang, C.; Huang, W.; Zhong, W.; Yi, J.; Feng, J.; Zouxu, X.; Song, L.; Wang, X. MANF facilitates breast cancer cell survival under glucose-starvation conditions via PRKN-mediated mitophagy regulation. *Autophagy* **2025**, *21*, 80–101. https://doi.org/10.1080/15548627.2024.2392415.
81. Zhang, S.; Chen, S.; Sun, D.; Li, S.; Sun, J.; Gu, Q.; Liu, P.; Wang, X.; Zhu, H.; Xu, X.; et al. TIN2-mediated reduction of mitophagy induces RPE senescence under high glucose. *Cell Signal* **2024**, *119*, 111188. https://doi.org/10.1016/j.cellsig.2024.111188.
82. Wu, D.; Huang, W.; Zhang, J.; He, L.; Chen, S.; Zhu, S.; Sang, Y.; Liu, K.; Hou, G.; Chen, B.; et al. Downregulation of VEGFA accelerates AGEs-mediated nucleus pulposus degeneration through inhibiting protective mitophagy in high glucose environments. *Int. J. Biol. Macromol.* **2024**, *262*, 129950. https://doi.org/10.1016/j.ijbiomac.2024.129950.
83. Yang, W.; Qiu, C.; Lv, H.; Zhang, Z.; Yao, T.; Huang, L.; Wu, G.; Zhang, X.; Chen, J.; He, Y. Sirt3 Protects Retinal Pigment Epithelial Cells From High Glucose-Induced Injury by Promoting Mitophagy Through the AMPK/mTOR/ULK1 Pathway. *Transl. Vis. Sci. Technol.* **2024**, *13*, 19. https://doi.org/10.1167/tvst.13.3.19.
84. Lee, H.; Cho, S.; Kim, M.J.; Park, Y.J.; Cho, E.; Jo, Y.S.; Kim, Y.S.; Lee, J.Y.; Thoudam, T.; Woo, S.H.; et al. ApoE4-dependent lysosomal cholesterol accumulation impairs mitochondrial homeostasis and oxidative phosphorylation in human astrocytes. *Cell Rep.* **2023**, *42*, 113183. https://doi.org/10.1016/j.celrep.2023.113183.
85. Wang, W.; Zhang, Y.; Huang, W.; Yuan, Y.; Hong, Q.; Xie, Z.; Li, L.; Chen, Y.; Li, X.; Meng, Y. Alamandine/MrgD axis prevents TGF-β1-mediated fibroblast activation via regulation of aerobic glycolysis and mitophagy. *J. Transl. Med.* **2023**, *21*, 24. https://doi.org/10.1186/s12967-022-03837-2.
86. Dai, T.; Zhang, X.; Li, M.; Tao, X.; Jin, M.; Sun, P.; Zhou, Q.; Jiao, L. Dietary vitamin K(3) activates mitophagy, improves antioxidant capacity, immunity and affects glucose metabolism in Litopenaeus vannamei. *Food Funct.* **2022**, *13*, 6362–6372. https://doi.org/10.1039/d2fo00865c.

87. Li, S.; Wang, Y.; Zhang, X.; Xiong, X.; Zhou, F.; Li, X.; Fan, J.; Liang, X.; Li, G.; Peng, Y.; et al. Mitochondrial damage-induced abnormal glucose metabolism with ageing in the hippocampus of APP/PS1 mice. *Metabolomics* **2023**, *19*, 56. https://doi.org/10.1007/s11306-023-02023-9.
88. Li, Z.; Meng, X.; Ma, G.; Liu, W.; Li, W.; Cai, Q.; Wang, S.; Huang, G.; Zhang, Y. Increasing brain glucose metabolism by ligustrazine piperazine ameliorates cognitive deficits through PPARγ-dependent enhancement of mitophagy in APP/PS1 mice. *Alzheimers Res. Ther.* **2022**, *14*, 150. https://doi.org/10.1186/s13195-022-01092-7.
89. Su, D.; Song, Y.; Li, D.; Yang, S.; Zhan, S.; Zhong, T.; Guo, J.; Cao, J.; Li, L.; Zhang, H.; et al. Cold exposure affects glucose metabolism, lipid droplet deposition and mitophagy in skeletal muscle of newborn goats. *Domest. Anim. Endocrinol.* **2024**, *88*, 106847. https://doi.org/10.1016/j.domaniend.2024.106847.
90. Li, Y.; Gao, Y.; Yu, G.; Ye, Y.; Zhu, H.; Wang, J.; Li, Y.; Chen, L.; Gu, L. G6PD protects against cerebral ischemia-reperfusion injury by inhibiting excessive mitophagy. *Life Sci.* **2025**, *362*, 123367. https://doi.org/10.1016/j.lfs.2024.123367.
91. Yuan, M.; Yao, Y.; Wu, D.; Zhu, C.; Dong, S.; Tong, X. Pannexin1 inhibits autophagy of cisplatin-resistant testicular cancer cells by mediating ATP release. *Cell Cycle* **2022**, *21*, 1651–1661. https://doi.org/10.1080/15384101.2022.2060655.
92. Junfang, Y.; Yi, X.; Fang, W.; Yuhong, C.; Jinhua, Z.; Zhihui, D.; Lu, G.; Hongyan, L.; Jing, S.; Chao, S.; et al. Carbon ion combined with tigecycline inhibits lung cancer cell proliferation by inducing mitochondrial dysfunction. *Life Sci.* **2020**, *263*, 118586. https://doi.org/10.1016/j.lfs.2020.118586.
93. Yidan, W.; Isabelle, M.; Yuting, M.; Oliver, K.; Lorenzo, G.; Guido, K. Autophagy-dependent ATP release from dying cells via lysosomal exocytosis. *Autophagy* **2013**, *9*, 1624–1625. https://doi.org/10.4161/auto.25873.
94. Michaud, M.; Martins, I.; Sukkurwala, A.; Adjemian, S.; Ma, Y.; Pellegatti, P.; Shen, S.; Kepp, O.; Scoazec, M.; Mignot, G.; et al. Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. *Science* **2011**, *334*, 1573–1577. https://doi.org/10.1126/science.1208347.
95. Peynshaert, K.; Manshian, B.; Joris, F.; Braeckmans, K.; De Smedt, S.; Demeester, J.; Soenen, S. Exploiting intrinsic nanoparticle toxicity: The pros and cons of nanoparticle-induced autophagy in biomedical research. *Chem. Rev.* **2014**, *114*, 7581–7609. https://doi.org/10.1021/cr400372p.
96. Naoki, I.; Urs, T.R.; Shin'ichi, T. ATP-Induced Increase in Intracellular Calcium Levels and Subsequent Activation of mTOR as Regulators of Skeletal Muscle Hypertrophy. *Int. J. Mol. Sci.* **2018**, *19*, 2804. https://doi.org/10.3390/ijms19092804.
97. Bian, S.; Sun, X.; Bai, A.; Zhang, C.; Li, L.; Enjyoji, K.; Junger, W.G.; Robson, S.C.; Wu, Y. P2X7 integrates PI3K/AKT and AMPK-PRAS40-mTOR signaling pathways to mediate tumor cell death. *PLoS ONE* **2013**, *8*, e60184–e60184. https://doi.org/10.1371/journal.pone.0060184.
98. Jiang, Y.; Lin, J.; Zheng, H.; Zhu, P. The Role of Purinergic Signaling in Heart Transplantation. *Front. Immunol.* **2022**, *13*, 826943. https://doi.org/10.3389/fimmu.2022.826943.
99. Yin, H.; Tang, X.; Peng, Y.; Wen, H.; Yang, H.; Li, S.; Zheng, X.; Xiong, Y. Pannexin-1 regulation of ATP release promotes the invasion of pituitary adenoma. *J. Endocrinol. Investig.* **2025**, *48*, 317–332. https://doi.org/10.1007/s40618-024-02445-9.
100. Bartlett, P.J.; Gaspers, L.D.; Pierobon, N.; Thomas, A.P. Calcium-dependent regulation of glucose homeostasis in the liver. *Cell Calcium* **2014**, *55*, 306–316. https://doi.org/10.1016/j.ceca.2014.02.007.
101. Kania, E.; Pająk, B.; Orzechowski, A. Calcium homeostasis and ER stress in control of autophagy in cancer cells. *Biomed. Res. Int.* **2015**, *2015*, 352794. https://doi.org/10.1155/2015/352794.
102. Høyer-Hansen, M.; Jäättelä, M. Connecting endoplasmic reticulum stress to autophagy by unfolded protein response and calcium. *Cell Death Differ.* **2007**, *14*, 1576–1582. https://doi.org/10.1038/sj.cdd.4402200.
103. Kondratskyi, A.; Yassine, M.; Kondratska, K.; Skryma, R.; Slomianny, C.; Prevarskaya, N. Calcium-permeable ion channels in control of autophagy and cancer. *Front. Physiol.* **2013**, *4*, 272. https://doi.org/10.3389/fphys.2013.00272.
104. Cárdenas, C.; Miller, R.A.; Smith, I.; Bui, T.; Molgó, J.; Müller, M.; Vais, H.; Cheung, K.H.; Yang, J.; Parker, I.; et al. Essential regulation of cell bioenergetics by constitutive InsP3 receptor Ca^{2+} transfer to mitochondria. *Cell* **2010**, *142*, 270–283. https://doi.org/10.1016/j.cell.2010.06.007.
105. Yuan, Y.H.; Yan, W.F.; Sun, J.D.; Huang, J.Y.; Mu, Z.; Chen, N.H. The molecular mechanism of rotenone-induced α-synuclein aggregation: Emphasizing the role of the calcium/GSK3β pathway. *Toxicol. Lett.* **2015**, *233*, 163–171. https://doi.org/10.1016/j.toxlet.2014.11.029.
106. Hoyer-Hansen, M.; Bastholm, L.; Szyniarowski, P.; Campanella, M.; Szabadkai, G.; Farkas, T.; Bianchi, K.; Fehrenbacher, N.; Elling, F.; Rizzuto, R.; et al. Control of macroautophagy by calcium, calmodulin-dependent kinase kinase-beta, and Bcl-2. *Mol. Cell* **2007**, *25*, 193–205. https://doi.org/10.1016/j.molcel.2006.12.009.
107. Shi, W.; Xu, D.; Gu, J.; Xue, C.; Yang, B.; Fu, L.; Song, S.; Liu, D.; Zhou, W.; Lv, J.; et al. Saikosaponin-d inhibits proliferation by up-regulating autophagy via the CaMKKβ-AMPK-mTOR pathway in ADPKD cells. *Mol. Cell. Biochem.* **2018**, *449*, 219–226. https://doi.org/10.1007/s11010-018-3358-0.
108. Félix-Martínez, G.J.; Godínez-Fernández, J.R. Mathematical models of electrical activity of the pancreatic β-cell: A physiological review. *Islets* **2014**, *6*, e949195. https://doi.org/10.4161/19382014.2014.949195.

109. Zhang, N.; Liu, F.; Zhao, Y.; Sun, X.; Wen, B.; Lu, J.Q.; Yan, C.; Li, D. Defect in degradation of glycogenin-exposed residual glycogen in lysosomes is the fundamental pathomechanism of Pompe disease. *J. Pathol.* **2024**, *Online ahead of print*. https://doi.org/10.1002/path.6255.
110. Kalamidas, S.A.; Kotoulas, O.B.; Hann, A.C. Studies on glycogen autophagy: Effects of phorbol myristate acetate, ionophore A23187, or phentolamine. *Microsc. Res. Tech.* **2002**, *57*, 507–511. https://doi.org/10.1002/jemt.10104.
111. Santoni, G.; Santoni, M.; Nabissi, M. Functional role of T-type calcium channels in tumour growth and progression: Prospective in cancer therapy. *Br. J. Pharmacol.* **2012**, *166*, 1244–1246. https://doi.org/10.1111/j.1476-5381.2012.01908.x.
112. Andrea, W.; Sovan, S.; Paul, C.; Evangelia, K.T.; Shinji, S.; Farah, H.S.; Luca, J.; Angeleen, F.; Dean, P.; Paul, G.; et al. Novel targets for Huntington's disease in an mTOR-independent autophagy pathway. *Nat. Chem. Biol.* **2008**, *4*, 295–305. https://doi.org/10.1038/nchembio.79.
113. Busch Sørensen, M.; Sjøstrand, H.; Sengeløv, H.; Tiefenthal Thrane, M.; Juul Holst, J.; Lyngsøe, J. Influence of short term verapamil treatment on glucose metabolism in patients with non-insulin dependent diabetes mellitus. *Eur. J. Clin. Pharmacol.* **1991**, *41*, 401–404. https://doi.org/10.1007/bf00626359.
114. Ardizzone, T.D.; Lu, X.H.; Dwyer, D.S. Calcium-independent inhibition of glucose transport in PC-12 and L6 cells by calcium channel antagonists. *Am. J. Physiol. Cell Physiol.* **2002**, *283*, C579–C586. https://doi.org/10.1152/ajpcell.00451.2001.
115. Pajak, B.; Kania, E.; Gajkowska, B.; Orzechowski, A. Verapamil-induced autophagy-like process in colon adenocarcinoma COLO 205 cells; the ultrastructural studies. *Pharmacol. Rep.* **2012**, *64*, 991–996. https://doi.org/10.1016/s1734-1140(12)70896-4.
116. Tomar, D.; Elrod, J.W. Metabolite regulation of the mitochondrial calcium uniporter channel. *Cell Calcium* **2020**, *92*, 102288. https://doi.org/10.1016/j.ceca.2020.102288.
117. Gray, L.R.; Sultana, M.R.; Rauckhorst, A.J.; Oonthonpan, L.; Tompkins, S.C.; Sharma, A.; Fu, X.; Miao, R.; Pewa, A.D.; Brown, K.S.; et al. Hepatic Mitochondrial Pyruvate Carrier 1 Is Required for Efficient Regulation of Gluconeogenesis and Whole-Body Glucose Homeostasis. *Cell Metab.* **2015**, *22*, 669–681. https://doi.org/10.1016/j.cmet.2015.07.027.
118. Nemani, N.; Dong, Z.; Daw, C.C.; Madaris, T.R.; Ramachandran, K.; Enslow, B.T.; Rubannelsonkumar, C.S.; Shanmughapriya, S.; Mallireddigari, V.; Maity, S.; et al. Mitochondrial pyruvate and fatty acid flux modulate MICU1-dependent control of MCU activity. *Sci. Signal* **2020**, *13*, eaaz6206. https://doi.org/10.1126/scisignal.aaz6206.
119. Fan, Y.; Wang, N.; Rocchi, A.; Zhang, W.; Vassar, R.; Zhou, Y.; He, C. Identification of natural products with neuronal and metabolic benefits through autophagy induction. *Autophagy* **2017**, *13*, 41–56. https://doi.org/10.1080/15548627.2016.1240855.
120. Goginashvili, A.; Zhang, Z.; Erbs, E.; Spiegelhalter, C.; Kessler, P.; Mihlan, M.; Pasquier, A.; Krupina, K.; Schieber, N.; Cinque, L.; et al. Insulin granules. Insulin secretory granules control autophagy in pancreatic β cells. *Science* **2015**, *347*, 878–882. https://doi.org/10.1126/science.aaa2628.
121. Rutter, G.A. Cell biology. Pancreas micromanages autophagy. *Science* **2015**, *347*, 826–827. https://doi.org/10.1126/science.aaa6810.
122. Yamamoto, S.; Kuramoto, K.; Wang, N.; Situ, X.; Priyadarshini, M.; Zhang, W.; Cordoba-Chacon, J.; Layden, B.; He, C. Autophagy Differentially Regulates Insulin Production and Insulin Sensitivity. *Cell Rep.* **2018**, *23*, 3286–3299. https://doi.org/10.1016/j.celrep.2018.05.032.
123. Bartolome, A.; Guillen, C.; Benito, M. Autophagy plays a protective role in endoplasmic reticulum stress-mediated pancreatic β cell death. *Autophagy* **2012**, *8*, 1757–1768. https://doi.org/10.4161/auto.21994.
124. Sheng, Q.; Xiao, X.; Prasadan, K.; Chen, C.; Ming, Y.; Fusco, J.; Gangopadhyay, N.N.; Ricks, D.; Gittes, G.K. Autophagy protects pancreatic beta cell mass and function in the setting of a high-fat and high-glucose diet. *Sci. Rep.* **2017**, *7*, 16348. https://doi.org/10.1038/s41598-017-16485-0.
125. Bachar-Wikstrom, E.; Wikstrom, J.D.; Ariav, Y.; Tirosh, B.; Kaiser, N.; Cerasi, E.; Leibowitz, G. Stimulation of autophagy improves endoplasmic reticulum stress-induced diabetes. *Diabetes* **2013**, *62*, 1227–1237. https://doi.org/10.2337/db12-1474.
126. Wang, P.; Li, J.; Li, C.G.; Zhou, X.; Chen, X.; Zhu, M.; Wang, H. Restoring Autophagy by Exercise Ameliorates Insulin Resistance Partly via Calcineurin-Driven TFEB Nuclear Translocation. *Clin. Exp. Pharmacol. Physiol.* **2025**, *52*, e70010. https://doi.org/10.1111/1440-1681.70010.
127. Luan, B.; Sun, C. MiR-138-5p affects insulin resistance to regulate type 2 diabetes progression through inducing autophagy in HepG2 cells by regulating SIRT1. *Nutr. Res.* **2018**, *59*, 90–98. https://doi.org/10.1016/j.nutres.2018.05.001.
128. Kang, Y.H.; Cho, M.H.; Kim, J.Y.; Kwon, M.S.; Peak, J.J.; Kang, S.W.; Yoon, S.Y.; Song, Y. Impaired macrophage autophagy induces systemic insulin resistance in obesity. *Oncotarget* **2016**, *7*, 35577–35591. https://doi.org/10.18632/oncotarget.9590.
129. Cai, J.; Pires, K.M.; Ferhat, M.; Chaurasia, B.; Buffolo, M.A.; Smalling, R.; Sargsyan, A.; Atkinson, D.L.; Summers, S.A.; Graham, T.E.; et al. Autophagy Ablation in Adipocytes Induces Insulin Resistance and Reveals Roles for Lipid Peroxide and Nrf2 Signaling in Adipose-Liver Crosstalk. *Cell Rep.* **2018**, *25*, 1708–1717.e1705. https://doi.org/10.1016/j.celrep.2018.10.040.
130. Rovira-Llopis, S.; Diaz-Morales, N.; Banuls, C.; Blas-Garcia, A.; Polo, M.; Lopez-Domenech, S.; Jover, A.; Rocha, M.; Hernandez-Mijares, A.; Victor, V.M. Is Autophagy Altered in the Leukocytes of Type 2 Diabetic Patients? *Antioxid. Redox Signal.* **2015**, *23*, 1050–1056. https://doi.org/10.1089/ars.2015.6447.

131. Song, R.; Zhao, X.; Cao, R.; Liang, Y.; Zhang, D.Q.; Wang, R. Irisin improves insulin resistance by inhibiting autophagy through the PI3K/Akt pathway in H9c2 cells. *Gene* **2021**, *769*, 145209. https://doi.org/10.1016/j.gene.2020.145209.
132. Kim, K.H.; Jeong, Y.T.; Oh, H.; Kim, S.H.; Cho, J.M.; Kim, Y.N.; Kim, S.S.; Kim, D.H.; Hur, K.Y.; Kim, H.K.; et al. Autophagy deficiency leads to protection from obesity and insulin resistance by inducing Fgf21 as a mitokine. *Nat. Med.* **2013**, *19*, 83–92. https://doi.org/10.1038/nm.3014.
133. Li, S.; Li, H.; Yang, D.; Yu, X.; Irwin, D.M.; Niu, G.; Tan, H. Excessive Autophagy Activation and Increased Apoptosis Are Associated with Palmitic Acid-Induced Cardiomyocyte Insulin Resistance. *J. Diabetes Res.* **2017**, *2017*, 2376893. https://doi.org/10.1155/2017/2376893.
134. Feng, J.; Li, J.; Wu, L.; Yu, Q.; Ji, J.; Wu, J.; Dai, W.; Guo, C. Emerging roles and the regulation of aerobic glycolysis in hepatocellular carcinoma. *J. Exp. Clin. Cancer Res. CR* **2020**, *39*, 126. https://doi.org/10.1186/s13046-020-01629-4.
135. Prieto-Dominguez, N.; Ordonez, R.; Fernandez, A.; Garcia-Palomo, A.; Muntane, J.; Gonzalez-Gallego, J.; Mauriz, J.L. Modulation of Autophagy by Sorafenib: Effects on Treatment Response. *Front. Pharmacol.* **2016**, *7*, 151. https://doi.org/10.3389/fphar.2016.00151.
136. Yan, X.; Tian, R.; Sun, J.; Zhao, Y.; Liu, B.; Su, J.; Li, M.; Sun, W.; Xu, X. Sorafenib-Induced Autophagy Promotes Glycolysis by Upregulating the p62/HDAC6/HSP90 Axis in Hepatocellular Carcinoma Cells. *Front. Pharmacol.* **2021**, *12*, 788667. https://doi.org/10.3389/fphar.2021.788667.
137. Cao, B.; Deng, H.; Cui, H.; Zhao, R.; Li, H.; Wei, B.; Chen, L. Knockdown of PGM1 enhances anticancer effects of orlistat in gastric cancer under glucose deprivation. *Cancer Cell Int.* **2021**, *21*, 481. https://doi.org/10.1186/s12935-021-02193-3.
138. Peng, H.; Wang, Q.; Qi, X.; Wang, X.; Zhao, X. Orlistat induces apoptosis and protective autophagy in ovarian cancer cells: Involvement of Akt-mTOR-mediated signaling pathway. *Arch. Gynecol. Obstet.* **2018**, *298*, 597–605. https://doi.org/10.1007/s00404-018-4841-2.
139. Sun, B.; Ou, H.; Ren, F.; Huan, Y.; Zhong, T.; Gao, M.; Cai, H.J.M.m. Propofol inhibited autophagy through Ca/CaMKKβ/AMPK/mTOR pathway in OGD/R-induced neuron injury. *Mol. Med.* **2018**, *24*, 58. https://doi.org/10.1186/s10020-018-0054-1.
140. Li, A.; Yi, B.; Han, H.; Yang, S.; Hu, Z.; Zheng, L.; Wang, J.; Liao, Q.; Zhang, H. Vitamin D-VDR (vitamin D receptor) regulates defective autophagy in renal tubular epithelial cell in streptozotocin-induced diabetic mice via the AMPK pathway. *Autophagy* **2022**, *18*, 877–890. https://doi.org/10.1080/15548627.2021.1962681.
141. Rim, H.K.; Cho, S.; Shin, D.H.; Chung, K.S.; Cho, Y.W.; Choi, J.H.; Lee, J.Y.; Lee, K.T. T-type Ca^{2+} channel blocker, KYS05090 induces autophagy and apoptosis in A549 cells through inhibiting glucose uptake. *Molecules* **2014**, *19*, 9864–9875. https://doi.org/10.3390/molecules19079864.