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Treatment of Metabolic Diseases by Modulating Autophagy: Current Strategies and Future Directions

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Abstract

As a key process in maintaining cellular metabolic homeostasis, the targeted regulation of autophagy offers new insights into the treatment of metabolic disorders such as diabetes, obesity, and non-alcoholic fatty liver disease (NAFLD). This systematic review examines core strategies for regulating autophagy to improve metabolic disorders, including lifestyle interventions, pharmacological modulation and the use of natural compounds. It also analyses the scientific basis and clinical limitations of existing therapies and explores future directions in tissue-specific drug development, precision medicine applications and interdisciplinary technological integration. The aim is to provide a theoretical foundation and practical reference for the development of safer and more effective metabolic disease treatments, facilitating a shift from broad-spectrum intervention to precise modulation.

Keywords

Autophagy, Metabolic Diseases, Lifestyle Intervention, Pharmacological Modulation

1. Introduction

Metabolic diseases are a group of chronic conditions caused by metabolic abnormalities. These conditions include type 2 diabetes mellitus (T2DM), obesity, and

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non-alcoholic fatty liver disease (NAFLD). Over the past two decades, the prevalence and mortality rates of metabolic diseases have increased significantly, imposing a substantial disease burden, particularly among males [1]. The prevalence of NAFLD, for example, is strongly associated with metabolic syndrome, and the risk of progression to cirrhosis and hepatocellular carcinoma is also increasing year by year [1] [2]. Meanwhile, the COVID-19 pandemic has further exposed the health vulnerabilities of patients with metabolic diseases, with significantly higher rates of severe illness and mortality after infection in this population, highlighting the complex interaction between metabolic disorders and immune imbalance [3]. Metabolic diseases pose a significant threat to global public health. Despite the emergence of novel therapies, such as gut flora modulation and epigenetically targeted treatments, gut flora modulation represents a novel therapeutic avenue. Microbial metabolites, such as short-chain fatty acids (e.g., butyrate), can directly signal to host intestinal and peripheral cells (including β-cells), activating autophagy pathways (e.g., via AMPK or HDAC inhibition) and thereby influencing metabolic health [4]. The global disease burden remains uncontrolled [1], and further breakthroughs are urgently needed from pathological mechanisms to clinical interventions [5] [6].

Autophagy is a highly conserved intracellular "cleaner" system that selectively removes damaged mitochondria, misfolded proteins, and excess lipid droplets via the lysosomal pathway, playing a central role in the regulation of metabolic homeostasis. Studies have shown that in metabolic diseases such as NAFLD, autophagy dysfunction forms a vicious circle with lipotoxicity, mitochondrial damage and inflammatory response. For example, in T2DM, dysregulation of autophagy, which maintains insulin secretion by removing aberrant protein aggregates (mainly composed of misfolded islet amyloid polypeptides (IAPP)) from β-cells, results in islet amyloid deposition and impaired glucose tolerance [7] [8]. In obesity models, autophagy deficiency in adipose tissue suppresses lipolysis and thermogenesis, exacerbating white adipose tissue expansion and systemic inflammation [9] [10]. In addition, metabolic abnormalities in the skeletal and cardiovascular systems are also closely related to autophagy imbalance, e.g., defective autophagy in osteoblasts triggered osteoporosis through impaired mitochondrial clearance [11], whereas dysregulated autophagy in cardiomyocytes exacerbates ischemia-reperfusion injury [12]. All of the above findings suggest that autophagy defects are important drivers of metabolic disorders and highlight the potential of targeting autophagic pathways for multi-organ therapy. Therefore, in-depth investigation of the relationship between autophagy regulation and the development of metabolic diseases will be of great significance for the prevention and treatment of metabolic diseases.

In this article, we summarize the core strategies for regulating autophagy in the treatment of metabolic diseases (including lifestyle intervention, pharmacological modulation, and the application of natural compounds), analyze the scientific basis and clinical limitations of the existing therapies, and explore the future direction of tissue-specific drug development, precision medicine application, and interdisciplinary technology integration, with the aim of providing theoretical basis and practical reference for the development of safer and more effective therapeutic options for metabolic diseases.

2. Lifestyle Intervention: Caloric Restriction

Decreased activity of autophagy, as one of the core mechanisms for cellular removal of damaged components and maintenance of energy homeostasis, is closely associated with metabolic disorders [13] [14]. Caloric Restriction (CR), as a non-pharmacological intervention to activate the autophagy pathway through a multidimensional signaling network, has become one of the important strategies to ameliorate metabolic diseases [15] [16]. Studies have shown that CR can directly upregulate the expression of autophagy-related proteins (e.g., LC3, Beclin1) and improves mitochondrial function by inhibiting the mammalian target of rapamycin protein complex 1 (mTORC1) signaling axis and activating the adenylate-activated protein kinase (AMPK) pathway [15]. In peripheral blood mononuclear cells from obese patients, CR intervention significantly enhanced AMPK activity and reduced mitochondrial reactive oxygen species (ROS) levels, accompanied by up-regulation of the expression of mitochondrial kinetic-related proteins (MFN2, DRP1, FIS1), suggesting that CR synergizes with mitochondrial autophagy to activate autophagic flow through energy induction [15]. In the Akt2 knockout mouse model, CR improved cardiac metabolic function by regulating the PINK1/Parkin pathway, and its elevated LC3-II/I ratio was positively correlated with the reduction of mitochondrial ROS, revealing a bidirectional regulatory mechanism of mitochondrial function and autophagy activity [17]. Notably, the metabolic protective effect of CR also involves the remodeling of neuroendocrine and intestinal flora. Animal studies have shown that hypothalamic neuropeptide Y (NPY) mimics the CR effect by enhancing CNS autophagic activity [18], whereas changes in the abundance of gut flora improve insulin sensitivity through the immune-metabolic axis [16]. In addition, CR exhibits specific effects in different metabolic tissues through autophagy modulation. In adipose tissue, CR combined with exercise training significantly reduced visceral fat mass percentage [19], up-regulated the expression of autophagy-related proteins such as ATG5 and ATG7 [20], and inhibited the abnormal accumulation of IgG to alleviate macrophage-mediated chronic inflammation [21]. In the liver, CR attenuates the lipotoxicity of NAFLD by up-regulating hepatic autophagy genes such as BECN1 and NBR1 and down-regulating pro-inflammatory gene expression [22] [23]. The cardiovascular system, on the other hand, reduces fibrosis after ischemia-reperfusion injury through CR-induced autophagy in cardiomyocytes and inhibits mTORC1 signaling to delay cardiac aging [12] [24] [25]. It is also important to note that there are significant gender and age differences in the metabolic effects of CR. Studies have shown that young male mice showed a more pronounced decrease in fat mass and improvement in insulin sensitivity after CR intervention, whereas female mice showed a weaker response [26], and altered miRNA expression profiles in the subcutaneous fat of middle-aged animals suggest that CR may delay metabolic aging through epigenetic regulation [27].

Although studies have shown that CR mimics (e.g., spermidine and 3,4-dimethoxychalcone) can activate autophagy and ameliorate the metabolic syndrome through pathways such as inhibition of IGF1R signaling [28] [29], prolonged or excessive CR may trigger problems such as excessive activation of autophagy leading to cell death [30]. Yadin *et al.* demonstrated that aberrant activation of autophagy aggravated cardiomyopathy [31], whereas cyclic CR patterns significantly improved cognitive function and intestinal health in aging mice [32], suggesting that autophagy intensity needs to be cautiously regulated in the context of specific diseases. Therefore, future studies need to combine the genetic background and metabolic status to formulate personalized protocols and deeply resolve the organ-specific mechanism of CR-regulated autophagy. The integration of artificial intelligence and multi-omics technologies may help to reveal the dynamic association of the CR-autophagy-metabolism network and provide theoretical support for the development of targeted intervention strategies, thus promoting caloric restriction as an important pillar of precision therapy for metabolic diseases.

3. Pharmacological Modulation of Autophagy

Table 1. Related drugs that modulate autophagy.

Drug name	Mechanism of action	Therapeutic effect	Research challenges	Future directions
Metformin	- Activates AMPK/mTOR pathway [33] [34] - Activate PINK1/Parkin mediated mitochondrial autophagy [35] - Enhancement of CMA [36]	- Improvement of diabetic β-cell function and glucose metabolism [8] - Anti-adipocyte hypertrophy and lipolysis [9] - Delayed vascular aging and atherosclerosis [37]	- Tissue-specific regulatory differences (e.g., liver and muscle) [13] [38] - Unknown epigenetic mechanisms of long-term "metabolic memory" [39] [40]	- Combination of autophagy enhancers/anti-inflammatory drugs - Single-cell sequencing and organoid modeling to study spatiotemporal heterogeneity - Epigenetic regulatory mechanisms resolved
SGLT2 inhibitor	- Inhibits mTORC1 signaling [41] - Activate AMPK/GSK3β pathway [42] [43] - Improvement of mitochondrial metabolism and oxidative stress [44] [45]	- Renal protection (reduction of podocyte apoptosis) [41] [46] [47] - Cardiovascular protection (inhibits myocardial fibrosis) [42] [45] [48] [49] - Improvement of hepatic lipid metabolism in NAFLD [50]	- Specificity of autophagy targets in different tissues are unclear - Complex mechanisms of interaction between autophagy and other cell death	- Dynamic study of specific molecular targets - The mechanism of balance between autophagy and apoptosis/accessory death is analyzed. - Personalized combination therapy development
Rapamycin	- Inhibits mTORC1 signaling pathway [51] - Promote autophagy flow and restore mitochondrial function [52] [53]	- Restore insulin secretion in diabetic β-cells [8] - Alleviation of myocardial and hepatic lipotoxicity [52] [53]	- Dose-dependent double-edged sword effect (low-dose protection vs. high-dose toxicity) [54] [55] - Global inhibition of mTOR leading to metabolic disorders [51] [56]	- Targeted delivery systems (e.g. hepatic targeting) - Co-regulation with drugs such as metformin - Development of novel mTOR inhibitors (e.g. RapaLink1)

Currently, research on drug-regulated autophagy for the treatment of metabolic diseases primarily centers on metformin, SGLT2 inhibitors, and rapamycin. **Table 1** provides a summary of recent advances in the application of these three agents—metformin, SGLT2 inhibitors, and rapamycin—in the treatment of metabolic diseases.

3.1. Metformin

Metformin, as a first-line drug for T2DM, has been found to play a crucial role in the treatment of metabolic diseases by regulating autophagy in recent years. Its mechanism of action mainly involves multiple signaling pathways such as the AMPK/mTOR pathway, mitochondrial autophagy and molecular chaperone-mediated autophagy (CMA). Studies have shown that metformin significantly enhances cellular autophagy activity by activating AMPK and inhibiting mTOR signaling [33] [34]. The drug promotes autophagy, ameliorates oxidative stress-induced cellular senescence and enhances survival via the AMPK/mTOR pathway [33], a mechanism that has also been validated in myocardial ischemia-reperfusion injury and diabetic cardiomyopathy models [34]. In addition, metformin specifically modulates mitochondrial quality control: in a diabetic nephropathy model, it significantly ameliorated mitochondrial oxidative damage and renal fibrosis progression by restoring PINK1/Parkin-mediated mitochondrial autophagy [35], and its ability to activate mitochondrial-selective autophagy was confirmed by increased co-localization of LC3 with the mitochondrial marker protein TOM20 [57]. CMA is also an important pathway of its action. Metformin removes misfolded proteins by enhancing lysosome-dependent protein degradation, a mechanism that is not only applicable to metabolic diseases but also shows potential application in neurodegenerative diseases and cancer [36].

Metformin demonstrates multidimensional effects in the treatment of metabolic diseases. In diabetes and its complications, the drug alleviates endoplasmic reticulum stress and mitochondrial dysfunction by restoring autophagy in pancreatic β-cells, which in turn improves insulin secretion and glucose metabolism regulation [8]. In a high-fat diet-induced obesity model, its anti-adipocyte hypertrophy effect is closely related to the modulation of TM4SF5 protein expression to enhance autophagy-dependent lipolysis [9]. Metformin-dependent AMPK-activated autophagy inhibits lipid accumulation and inflammatory responses, thereby alleviating insulin resistance [9] [58]. In addition, the protective effect of metformin on the vascular system is supported by new evidence: in a vascular smooth muscle cell senescence model, it inhibits the expression of senescence markers such as p21 and p53 by restoring autophagic activity and reduces the release of pro-inflammatory factors, providing new insights into the slowing down of vascular ageing and atherosclerosis [37].

Current research for metformin is advancing towards precision. Experimental studies have shown that its combination with autophagy enhancers or anti-inflammatory drugs can produce a synergistic effect, inducing both autophagy and apoptosis [59], which provides new ideas for the combination therapy of metabolism-related diseases. However, although metformin activates autophagy in most tissues, metabolically critical organs such as the liver and muscle may show different modulatory effects due to differences in energy status [13] [38]. Therefore, tissue-specific regulation remains an important challenge. Another key issue is that the "metabolic memory" effect revealed the potential role of epigenetic regulation, such as AMPK-dependent activation of SIRT1 leading to histone deacetylation and altered expression of autophagy gene [60], as well as modulation of DNA methylation patterns in regulatory regions of these gene, and metformin may produce long-term autophagy regulation through DNA methylation or non-coding RNAs, but the specific molecular mechanisms still need to be explored [39] [40]. Future studies may combine single-cell sequencing and organoid models to systematically reveal the spatiotemporal heterogeneity of metformin-regulated autophagy, laying the foundation for the development of personalized therapeutic options for metabolic diseases.

3.2. SGLT2 Inhibitors

SGLT2 inhibitors (e.g., empagliflozin), as a novel class of hypoglycemic agents, reduce glucose reabsorption by inhibiting sodium-glucose cotransporter protein 2 (SGLT2) in renal proximal tubules. Their broad protective effects against the metabolic syndrome are closely related to autophagy modulation. Mechanistic studies have shown that SGLT2 inhibitors synergistically enhance autophagic activity through multiple pathways [41]-[43]. On the one hand, the inhibitory effect on autophagy is deregulated by inhibiting the mTORC1 signaling pathway [41]. On the other hand, energy metabolism is regulated by activating the AMPK/GSK3β pathway [42] [43]. SGLT2 inhibitors also indirectly restore the scavenging capacity of the autophagy-lysosome system by improving the homeostasis of mitochondrial energy metabolism, and their oxidative stress-reducing effects provide critical support for metabolic organ protection [44] [45].

Numerous studies have shown [42] [46]-[50] [61] that SGLT2 inhibitors exhibit multi-organ protective effects in the treatment of metabolic diseases. Animal experiments have shown that it significantly reduces podocyte apoptosis and glomerulosclerosis in diabetic mice, and the mechanism of action is directly related to the restoration of autophagy to inhibit mTORC1 overactivation [41] [46] [47]. In the cardiovascular system, the drug reduces myocardial fibrosis and oxidative damage in a diabetic cardiomyopathy model by inhibiting the activity of inflammatory vesicles such as NLRP3 and enhancing cardiomyocyte autophagy, and its cardioprotective effects are partially dependent on autophagy-mediated cell survival mechanisms [42] [45] [48] [49]. In addition, engeletin modulates autophagic activity in epicardial adipose tissue and reduces pro-inflammatory factor release to improve cardiac function [61]. For NAFLD, SGLT2 inhibitors, on the other hand, improve hepatic steatosis and insulin resistance by inhibiting hepatic O-GlcNAc glycosylation levels and activating hepatocyte autophagy to promote lipid droplet degradation and mitochondrial fatty acid oxidation [50]. Clinical translational studies further validated these findings [62] [63]. The underlying mechanisms of clinical benefit may involve autophagy-mediated multidimensional effects, including increased energy expenditure by promoting sympathetic innervation of adipose tissue [64], suppression of microglial inflammatory responses in neurodegenerative lesions [65], and modulation of renal tubular sodium-hydrogen exchanger (NHE3) activity to ameliorate disturbances in water and sodium metabolism, thereby indirectly attenuating cellular stress and autophagy imbalance [66] [67]. These findings suggest that the organ-protective effects of SGLT2 inhibitors may go beyond the pure glucose-lowering effect, and their autophagy-regulating ability will be important in the prevention and treatment of metabolic syndrome, but further clarification is needed. Future studies should focus on the following directions: first, to elucidate the specific molecular targets of SGLT2 inhibitors in regulating autophagy in different tissues (e.g., kidney, heart, and liver) and their spatial and temporal dynamic characteristics. Secondly, to analyze the interaction between autophagy and other forms of cell death (e.g., apoptosis, pyroptosis) under metabolic stress conditions, especially the dynamic equilibrium mechanism in cardiovascular and renal lesions. Thirdly, to develop individualized treatment strategies based on patient metabolic phenotypes (e.g., degree of insulin resistance, mitochondrial functional status) to maximize autophagy-mediated therapeutic benefits. And finally, exploring combination therapies of SGLT2 inhibitors with other autophagy activators (e.g., rapamycin) or anti-inflammatory drugs may open new avenues for synergistic treatment of metabolic syndrome. By integrating molecular mechanism studies and clinical translational evidence, the potential of SGLT2 inhibitors as "metabolism-autophagy modulators" is expected to be further explored, providing a new direction for the precision treatment of metabolic diseases.

3.3. Rapamycin

As a classical mTOR inhibitor, rapamycin has become an important tool in the study of autophagy and metabolic diseases by targeting the regulation of mTORC1 to release its inhibitory effect on autophagy. In diabetes models, rapamycin ameliorates insulin secretion defects by restoring β-cell autophagy [8], while alleviating high-fat diet-induced lipid accumulation in hepatocytes and promoting damaged mitochondrial clearance to maintain glucolipid metabolic homeostasis [68]. In a model of myocardial cytotoxic injury and metabolism-associated fatty liver disease (MAFLD), it reduces ROS accumulation and promotes ATP generation by restoring autophagic flux, thereby mitigating mitochondrial dysfunction and lipotoxic damage [52] [53]. However, its effects exhibit tissue specificity and sex differences. Studies have shown that intestinal cells in female mice are more sensitive to rapamycin-induced autophagy [69], suggesting that sex hormones may influence efficacy by modulating the mTOR signaling pathway.

Despite the metabolic protection of rapamycin, its global mTOR inhibition via rapamycin can lead to significant immunosuppression primarily by inhibiting antigen-induced T-cell proliferation and cytokine production, which also leads to a complex "double-edged sword" effect. Studies indicate that excessive inhibition of clinical mTORC1 in β-cells interferes with the physiological regulation of insulin secretion, leading to abnormal fluctuations of blood glucose in the fasting state [51], whereas weak inhibition of mTORC2 by rapamycin may trigger compensatory metabolic disorders [56]. Low doses of rapamycin induce protective autophagy, whereas high doses may lead to autophagosome accumulation and cytotoxicity by inhibiting lysosomal acidification [54] [55]. This dose-dependent paradoxical effect limits further applications of rapamycin. In addition, global modulation of metabolic networks by rapamycin may activate AMPK compensatory signaling, leading to fatty acid oxidation excess and muscle wasting, or even interfere with immune metabolism (e.g., inhibition of T-cell function), affecting its therapeutic window in diseases such as chronic inflammation [70] [71].

In response to these limitations, researchers are optimizing their potential for clinical application through multiple strategies. Tissue-specific delivery systems (e.g., GN3-engineered macrophage membrane-encapsulated delivery system) have demonstrated higher liver targeting and lower immunogenicity in MAFLD models [72]. Dynamic regulatory strategies [51] combined with co-administration (e.g., enhancing AMPK activity in combination with metformin) synergistically improve metabolic flexibility [73]. The next-generation mTOR inhibitor RapaLink1 demonstrated enhanced autophagy induction and lower risk of metabolic disorders in preclinical studies by simultaneously affecting the mTORC1/mTORC2 complex [74], whereas variant inhibitors target specific subcellularly-localized mTOR complexes for precise regulation [75]. In addition, the development of individualized therapeutic strategies such as screening of sensitive patient subtypes by detecting autophagy markers such as p62, LC3-II/I and mTORC1/2 activity (e.g., 4EBP1 levels) [76], and optimizing dosing regimens in combination with multi-omics profiling [77] are also noteworthy.

The potential and challenges of rapamycin in the treatment of metabolic diseases coexist, and its double-edged effect stems from the pivotal position of the mTOR pathway in the metabolic network and the complex feedback mechanism. Future research needs to integrate novel delivery technologies, dynamic regulatory strategies and multi-group biomarkers to promote its leap from basic research to precise clinical application and provide new ideas for targeted therapy of metabolic diseases.

4. Natural Compounds

Some natural compounds (e.g. resveratrol, inulin, catechins, etc.) may provide low-toxicity and synergistic therapeutic strategies for metabolic diseases by activating the AMPK/SIRT1 pathway or inhibiting mTOR signaling, enhancing autophagy activity, promoting degradation of lipid droplets and restoration of mitochondrial function, and ameliorating hepatic lipid accumulation and oxidative stress. Inulin is a group of natural polysaccharides, that has been shown to indirectly enhance hepatic autophagy to inhibit the progression of non-alcoholic steatohepatitis (NASH) by enriching Parabacteroides distasonis to produce pentadecanoic acid, restoring intestinal barrier function and reducing endotoxemia [78]. Resveratrol is a polyphenol that is believed to have anti-inflammatory and immunomodulatory activities. Animal experiments have shown that the administration of resveratrol induces autophagy in the organism, and the increase in the levels of the markers beclin-1 and Atg5 protein and the decrease in the expression of p62 are effective in preventing hepatic lipid accumulation [79]. Its potential to attenuate hepatocellular lipid accumulation and inflammation was also supported in a methionine-choline-deficient NASH model [80]. Further studies have shown that the combination of resveratrol and metformin also attenuates hepatic steatosis by activating autophagy and reducing lipid accumulation via the cAMP/AMPK/SIRT1 signaling pathway [81]. In addition, randomized controlled trials have shown that a green Mediterranean diet rich in polyphenols, such as catechins, also significantly reduces intrahepatic fat content, and its effect is closely related to autophagy-mediated lipid clearance [82]. Notably, some natural active ingredients may affect host metabolism by regulating gut flora metabolites (e.g., short-chain fatty acids) through targeted modulation of related proteins such as RPN11 and ACC1 [83]-[85], suggesting a multidimensional effect of natural compounds in ameliorating lipotoxicity and metabolic disorders. The above evidence suggests that natural compounds often achieve metabolic protection by synergistically modulating oxidative stress, mitochondrial metabolism and autophagy pathways, e.g. targeting ACC1 degradation or inhibition of RPN11 improves both insulin sensitivity and fibrotic progression [83]-[85].

However, the clinical application of natural compounds still faces many challenges. Low bioavailability is a major bottleneck. Studies have shown that the effects of resveratrol on hepatic steatosis are significantly hampered in the presence of autophagy inhibitors (3-methyladenine, Bafilomycin A1, and chloroquine) or interventions targeting autophagy-related genes (Atg5 or beclin-1), suggesting that the beneficial effects of resveratrol are closely linked to its regulation of autophagy [86] [87]. Individual heterogeneity (e.g. PNPLA3 I148M gene variant) and differences in gut flora also significantly affect efficacy [88] [89], and individualized regimens need to be developed based on genetic background and microbial composition analysis. In addition, excessive activation of autophagy may exacerbate tissue damage. For example, the multi-targeted effects of natural compounds may interfere with the dynamic balance between autophagy and other cell death pathways (e.g., apoptosis) under specific pathological conditions [87]. Future research needs to combine precision medicine with interdisciplinary technologies to break through existing limitations. The development of natural derivatives targeting key autophagy nodes (e.g., ULK1, LC3-II), combined with single-cell sequencing to resolve the dynamics of tissue-specific autophagy, is expected to achieve precise regulation. Secondly, synergistic gut-liver axis intervention strategies (e.g., combining prebiotics with polyphenolic compounds) may ameliorate metabolic disorders through the dual action of flora metabolites (pentadecanoic acid) and autophagy pathways [78]. Furthermore, the use of artificial intelligence-assisted drug design accelerates the high-throughput screening of natural compound libraries, e.g. using hepatocyte organoid models to predict multi-target synergistic effects, optimizing candidate molecules, and investigate their mechanisms and drug targets [88]. For clinical translation, stratified clinical trials based on biomarkers (e.g. plasma OxPLs) are needed to clarify the causal association between autophagy modulation and metabolic endpoints (e.g. liver fibrosis reversal) [90]. By integrating multi-omics technologies and delivery system innovations, natural compounds are expected to be upgraded from “dietary interventions” to “targeted autophagy drugs”, providing a new direction for personalized treatment of metabolic diseases.

5. Conclusions and Perspective

While autophagy, as a core regulatory mechanism of cellular metabolic homeostasis, shows immense potential in treating metabolic diseases, its clinical application faces multiple challenges and scientific controversies. While protective at basal levels, excessive or dysregulated autophagy can become cytotoxic. This can occur through crosstalk with apoptosis pathways (e.g., sustained Beclin-1 activation can promote apoptosis via Bcl-2 dissociation), or via impaired cellular function resulting from unrestrained mitophagy leading to bioenergetic failure [91]. The current study reveals that the “double-edged sword” effect of autophagy significantly limits its therapeutic window—for example, rapamycin ameliorates hepatic lipid accumulation through activation of autophagy [52] [53] [68], but its systemic mTOR inhibition may trigger decreased insulin sensitivity and immune suppression and immunosuppression [51] [56] [70] [71]. Whereas in NASH, over-activated autophagy may accelerate abnormal mitochondrial degradation and instead exacerbate oxidative stress and fibrosis [83]-[85] [92]. This paradoxical effect suggests that future drug development needs to focus on tissue-specific regulatory strategies (e.g., targeting hepatic lipophagy or myocardial mitochondrial autophagy) [93] [94] rather than global activation of autophagy pathways. In addition, population heterogeneity and differences in pathological mechanisms further increase therapeutic complexity. Hepatic lipotoxicity (e.g., activation of the diacylglycerol-PKC-ε pathway) may be preferentially ameliorated by autophagy modulation in obese patients [95], whereas β-cell dysfunction in diabetic patients may be attenuated by excessive autophagy leading to degradation of proteins associated with insulin secretion [7] [8] [51] [96] [97]. Genetic factors [88] [89] and gender differences (e.g., women are more sensitive to lifestyle interventions) [98] reinforce the need for individualized treatment strategies. Therefore, the integration of metabolic phenotypic stratification (e.g., hepatic fat content, insulin secretion capacity) with multiple groups of biomarkers (e.g., exosomal miR-690, plasma acetyl coenzyme A levels) will be a potential direction for precision therapy [89]

[95] [99] [100]. At the clinical translational level, innovation in autophagy activity detection technology remains a key issue. Existing methods rely on invasive biopsies or indirect indicators [101], which are unable to monitor autophagy flux dynamically. Despite the emerging potential of non-invasive detection technologies based on exosomal miRNA or imaging histology [94], their specificity and mechanistic relevance still need to be validated on a large scale. In the future, a standardized autophagy activity assessment system should be established, combined with artificial intelligence-assisted metabolic imaging analysis for dynamic optimization of therapeutic regimens.

Based on the above challenges, the clinical application of autophagy modulation still needs to seek breakthroughs in innovative strategies. In terms of interventions, priority should be given to promoting safer lifestyle interventions (e.g. caloric restriction/intermittent fasting) and optimizing existing drug combination regimens—e.g. combining metformin with GLP-1 receptor agonists to synergistically modulate autophagy through AMPK activation and enteroglycoprokinetic effects [102] [103], or developing tissue-specific delivery systems (e.g. liver-targeted ACC1 inhibitors [83] [84]) to reduce systemic side effects. At the technical level, there is a need to accelerate the development of novel modulators targeting key nodes of autophagy (e.g. ULK1, LC3-II) and to resolve tissue-specific regulatory networks using single-cell sequencing and organ-like models. In addition, stratified clinical trials based on genetic risk scores (e.g., PNPLA3 variants [89]) and metabolomic profiles will drive the shift from "broad-spectrum intervention" to "precision repair" in therapeutic strategies.

In summary, autophagy regulation opens up a promising new pathway for the treatment of metabolic diseases, but its clinical translation needs to strike a balance between mechanistic depth and therapeutic safety. Through interdisciplinary integration and innovative clinical study design, it is promising to make the leap from basic discovery to clinical benefit and provide safer and more effective personalized therapeutic solutions for metabolic syndrome patients.

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Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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