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Mechanisms and therapeutic implications of selective autophagy in nonalcoholic fatty liver disease

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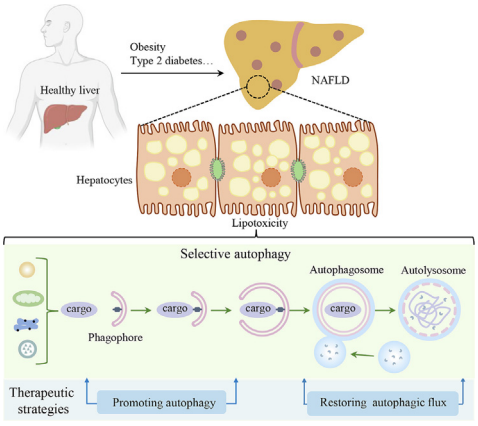
HIGHLIGHTS

- Lipophagy, mitophagy, reticulophagy and pexophagy are involved in the pathogenesis of NAFLD.
- Selective autophagic flux is impaired in NAFLD.
- Impaired autophagic-lysosomal fusion, perturbed lysosomal function, suppressed lysosomal biogenesis contribute to the impeded autophagic flux.
- Promoting selective autophagy and restoring autophagic flux are promising treatment strategies for NAFLD.
- Numerous medications and natural products promote selective autophagy to ameliorate NAFLD.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease worldwide, whereas there is no approved drug therapy due to its complexity. Studies are emerging to discuss the role of selective autophagy in the pathogenesis of NAFLD, because the specificity among the features of selective autophagy makes it a crucial process in mitigating hepatocyte damage caused by aberrant accumulation of dysfunctional organelles, for which no other pathway can compensate.

Aim of review: This review aims to summarize the types, functions, and dynamics of selective autophagy that are of particular importance in the initiation and progression of NAFLD. And on this basis, the review outlines the therapeutic strategies against NAFLD, in particular the medications and potential natural products that can modulate selective autophagy in the pathogenesis of this disease.

Key scientific concepts of review: The critical roles of lipophagy and mitophagy in the pathogenesis of NAFLD are well established, while reticulophagy and pexophagy are still being identified in this disease due to the insufficient understanding of their molecular details. As gradual blockage of autophagic flux reveals the complexity of NAFLD, studies unraveling the underlying mechanisms have made it possible to successfully treat NAFLD with multiple pharmacological compounds that target associated pathways.

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Overall, it is convinced that the continued research into selective autophagy occurring in NAFLD will further enhance the understanding of the pathogenesis and uncover novel therapeutic targets.
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Contents

Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of triglycerides ≥5 % in the hepatic tissue (i.e. steatosis), in the absence of excessive alcohol consumption and other competing liver disorders such as chronic viral hepatitis or administration of steatogenic medications [1]. The disease spectrum includes nonalcoholic simple fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC). In less than 40 years, NAFLD has become the most common chronic liver disease worldwide [2], affecting approximately 25 % of adults [3]. The global prevalence of NAFLD is now estimated to be 32.4 %, and is still increasing [4].

The mechanisms that contribute to the onset of NAFLD are complicated, and the two-hit hypothesis was originally proposed [5]. This theory proposes that sedentary behavior, high-fat diets (HFD), and obesity lead to lipid accumulation and insulin resistance, which is the first hit. The second hit refers to the generation of a large amount of reactive oxygen species (ROS) caused by excessive lipid accumulation, which leads to a series of changes such as oxidative stress and aggregation of inflammatory factors, allowing the disease progress to NASH, even cirrhosis and HCC. In recent years, researchers made intensive studies on NAFLD, and brought up a more convincing theory of "multiple hit" [6]. This theory proposes that the pathogenesis of NAFLD involves multiple parallel events, including gut microbiota imbalance, insulin resistance, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, inflammatory cytokines aggregation, as well as genetic/epigenetic risk factors, among others. They have synergistic and superimposed effects, leading to hepatocyte injury and promoting the initiation and progression of NAFLD. In this process, the defective organelles, including lipid droplets, mitochondria, ER, peroxisomes, accumulate in the cell, and degradation systems such as autophagy are clearly needed to dispose of these detrimental cellular components. Nowadays, a growing number of studies have recognized that autophagic disturbance is closely related to the development of NAFLD, and targeting autophagy represents a promising strategy for the prevention and treatment of NAFLD [7].

Autophagy, derived from the Greek word for "self-eating", refers to the catabolic process by which cells process their constituents [8]. Currently, three main types of autophagy have been identified: macroautophagy, microautophagy, and chaperone-mediated autophagy. In macroautophagy, hereinafter referred to as autophagy, cytoplasmic "cargo" is sequestered by a double-membrane structure, also known as phagophore, which extends to form a completed autophagosome. Subsequently, the autophagosome fuses with the lysosomes, where the cargo is degraded by acid hydrolases and lipases [9–11]. Based on the cargo specificity, autophagy can be divided into non-selective autophagy and selective autophagy. The latter is a well-orchestrated process consisting of tagging, identification, engulfment and degradation of specific substrates, particularly dysfunctional or superfluous organelles [12,13]. The specificity among the features of selective autophagy makes it a crucial process in mitigating hepatocyte damage caused by aberrant accumulation of dysfunctional organelles in the pathogenesis of NAFLD, with no other system replacing it. It has been shown that the selective autophagy involved in NAFLD includes lipophagy, mitophagy, reticulophagy and pexophagy (Fig. 1). This review will focus on the types, functions and dynamics of selective autophagy that are of particular importance in the initiation and progression of NAFLD, as well as the potential drugs targeting different types of selective autophagy.

Types of selective autophagy occurring in NAFLD

Lipophagy

To reduce their cell toxicity, free fatty acids (FFAs) can be esterified into neutral lipids, such as triglycerides (TG) and cholesterol (CHO), in the ER. When neutral lipids accumulate in excess between the ER membranes, they are stored in the form of lipid droplets (LDs). Excessive intake of FFAs results in adverse accumu-

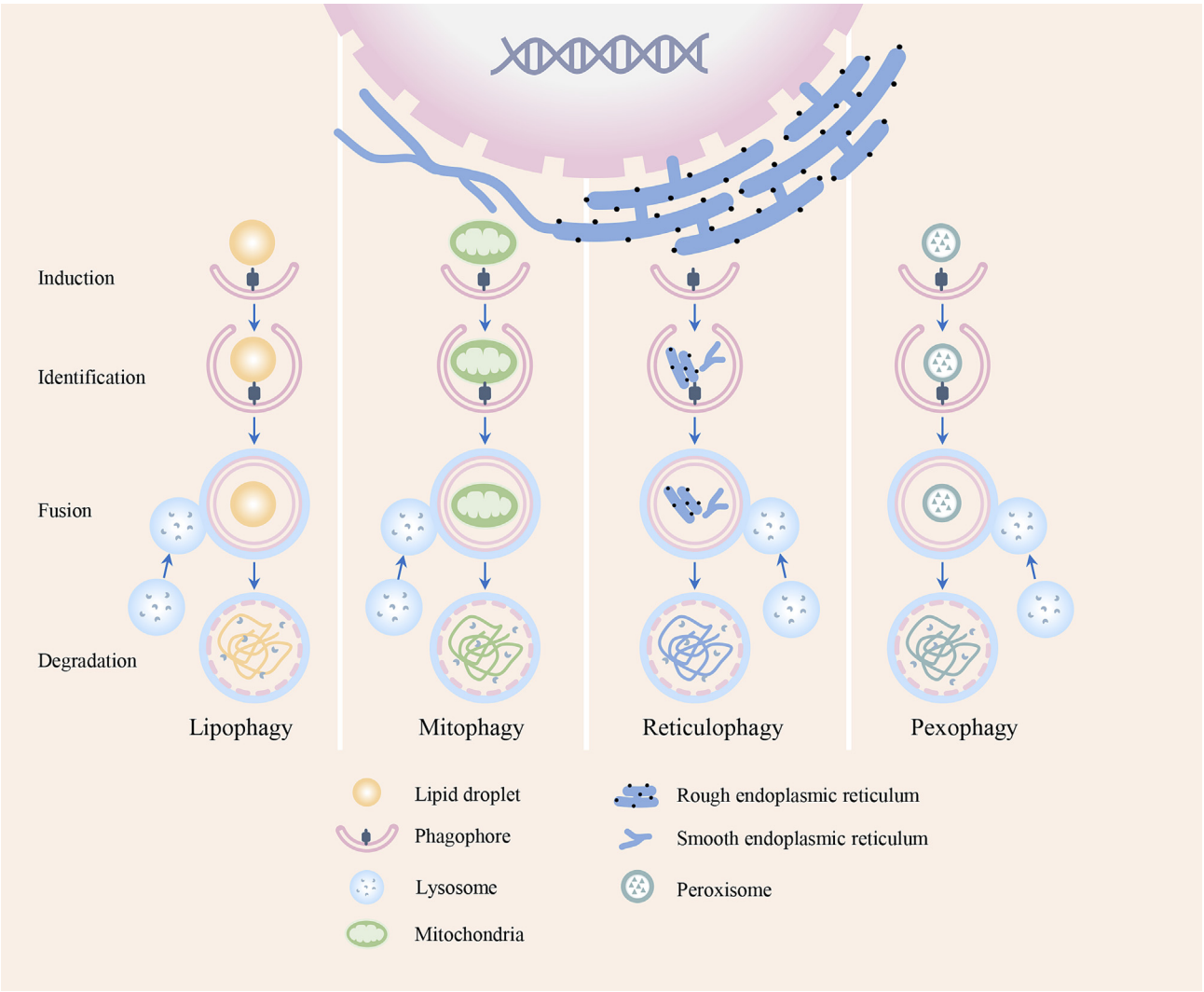

Fig. 1. The process of selective autophagy in NAFLD. Excess or damaged lipid droplets, mitochondria, endoplasmic reticulum, and peroxisomes are recognized by selective autophagy receptors, which bind to phagophores with the LC3/GABARAP family proteins. The phagophores extend and seal to form autophagosomes which subsequently fuse with the lysosomes for degradation.

lation of LDs and lipotoxicity in hepatocytes, which is a prerequisite for the occurrence of NAFLD [14,15]. Therefore, timely clearance of LDs is crucial for maintaining liver function. Previously, lipolysis, which is a biochemical pathway that relies on the direct activation of LD-associated lipases, were widely considered to be the main metabolic pathway of LDs [16]. Lipophagy has recently been described as an alternative mechanism to mobilize of LDs in the liver. Similar to the previously described macroautophagy process, in lipophagy, the autophagosomes containing LC3 may directly target selective receptors on the periphery of LDs to envelop them; thereafter, the LD-carrying autophagosomes fuse with lysosomes to catabolize the LDs in the presence of lysosomal acid lipases [17,18]. Previous pre-clinical studies have suggested that lipophagy is impaired in the livers of mice fed with HFD for four months [17], which may be associated with the high levels of methionine and S-adenosylmethionine in the circulation [19]. It has also been found that disease progression in NAFLD patients correlate with lipophagy dysfunction [20]. However, a recent study has established that oleic acid treatment activates lipophagy in primary hepatocytes. Activation of lipophagy is also observed in the livers of mice fed with HFD for one month [21]. Regarding the controversy, an intriguing possibility is that the state of lipophagy varies depending on the stage of NAFLD.

Theoretically, lipolysis reduces the aberrant accumulation of LDs to alleviate NAFLD. However, in practice, activation of lipolysis exacerbates the disease because of the toxicity of the liberated fatty acids [22,23]. In contrast, there is clear evidence that lipophagy activation can resist lipid-driven hepatotoxicity in NAFLD [24,25]. Studies using synthetic adaptor proteins to induce selective lipophagy have shown that lipophagy lowers the intracellular fatty acid content through lysosomal exocytosis rather than catabolizing the lipids in hepatocytes [26]. However, we currently have very limited insight into the molecular details of how lipophagy is initiated and carried out, especially how the specificity is achieved. Therefore, identification of the selective receptors involved in the occurrence of lipophagy would be of great significance for the treatment of NAFLD.

In the absence of selective autophagy receptors for lipophagy, several studies have demonstrated that p62, which is a well-established ubiquitin-binding autophagy receptor, interacts with some LD-localized proteins and acts as a lipophagy receptor [27,28]. For example, perilipin 2 (PLIN2), which is a predominate LD surface protein, was found to co-immunoprecipitate with p62 in a skeletal muscle cell line [29]; however, PLIN2 deficiency enhanced autophagy in the liver and alleviated fatty liver disease [30], suggesting the complexity of the lipophagy machinery

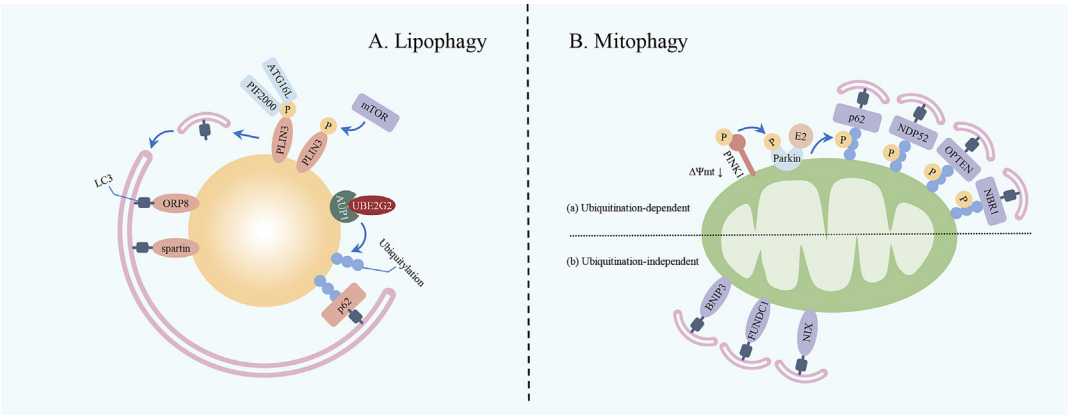

Fig. 2. Proposed models of key molecular events mediating lipophagy and mitophagy in NAFLD. (**A)** Lipophagy: mTORC1 phosphorylates PLIN3 to promote autophagosome formation. p62, ORP8 and spartin act as lipophagy receptor to directly interact with LC3/GABARAPs thus delivering LDs to lysosomes. AUP1 recruits and binds to ubiquitin conjugating enzyme E2 G2 (UBE2G2) to promote ubiquitination, which may be involved in liphophagy. (**B)** Mitophagy: When membrane potential (ΔΨ) decreased in response to mitochondrial damage, PINK1 accumulates at outer mitochondrial membrane (OMM), where it mediates ubiquitin phosphorylation and the recruitment and activation of E3 ubiquitin ligase Parkin, thus leading to increased conjugation of ubiquitin chains on the OMM. Then adaptor proteins such as p62, NDP52, OPTEN and NBR1 bind to the polyubiquitin chains and thus serve as bridges between the dysfunctional mitochondria and the nascent phagophore (a). Selective receptors such as BNIP3, FUNDC1 and NIX directly link the mitochondria to autophagic machinery by binding to LC3 (b).

in vivo. Similarly, perilipin 1 (PLIN1), which is another LD surface protein of the same family as PLIN2, has been demonstrated to be ubiquitinated and recognized by p62 in 293T cells [31]. Other ubiquitin-related proteins, such as ancient ubiquitous protein 1 (AUP1), which is widely expressed on the surface of LDs, recruit the ubiquitin conjugating enzyme E2 G2 (UBE2G2/UBC7) to the LDs and may participate in lipophagy [32]. Obviously, the limited understanding of how LDs are exclusively tagged and linked to the autophagic machinery makes the mechanism of lipophagy in NAFLD elusive. Recently, Garcia-Macia *et al.* attempted to address this issue and identified perilipin 3 (PLIN3) as a docking protein that induces lipophagy upon hepatic overload of oleic acid [21]. In addition, one study explicitly proposed that a lipid transfer protein ORP8, which is located on LDs, is a lipophagy receptor that interacts with LC3/GABARAP proteins through LC3 interaction regions (LIRs) for engulfment of LDs by autophagosomes [33]. In addition, Chung *et al.* have identified spartin, which is encoded by *SPART*, as a receptor that is localized to LDs and recruits autophagic vacuoles that carry LC3 through LIRs in ubiquitin-binding regions, thereby delivering LDs to lysosomes [34] (Fig. 2A). The physiological role of these selective receptor candidates, which are closely related with lipophagy, warrants further investigation and validation in the context of NAFLD.

Mitophagy

The liver is the main site for the oxidative decomposition of fatty acids. In hepatocytes, fatty acids are degraded through mitochondrial β-oxidation to provide energy for cells [35]. After being transported into the cytoplasm, FFAs are activated to form acyl-coenzyme A and enter into the mitochondria through carnitine palmitoyltransferase-1 to be gradually decomposed by β-oxidation. The acetoacetyl CoA produced in this process is thoroughly oxidized through the tricarboxylic acid cycle, and NAD^+ and FAD are used as hydrogen acceptors to generate NADH and FADH2. The electrons transported by NADH and FADH2 flow through the electron transport chain (ETC), which then creates an electrochemical gradient on the inner mitochondrial membrane (IMM) and ultimately synthesizes adenosine triphosphate (ATP) [36]. In general, 0.2 % to 2 % of the electrons are not correctly transferred in the ETC but spill off the chain and interact with oxygen to form ROS [37,38]. Under normal physiological conditions, the ROS generated along with ETC are cleared by enzymatic and nonenzymatic antioxidants to keep them at low levels and steady-state without causing cytotoxicity [39]. In NAFLD, mitochondrial fatty acid β-oxidation is enhanced adaptively in response to lipid accumulation secondary to the excessive FFAs flow into the liver. The consequent accumulation of massive electrons overwhelms the ETC and exacerbates ROS production, which finally leads to ETC dysfunction [40,41]. The impaired ETC function associated with increased β-oxidation rate leads to incomplete decomposition of fatty acids and accumulation of toxic lipid intermediates, which, together with excess ROS induce lipid peroxidation in the mitochondrial membrane, ultimately leading to mitochondrial damage. Impaired mitochondria augment ROS production and create a vicious cycle that contributes to hepatocyte cell death and inflammation, which in turn drives the development of NAFLD [42,43].

Damaged and dysfunctional mitochondria can be selectively eliminated by mitophagy, which is a specific type of autophagy that transports the targeted mitochondria to lysosomes for degradation, thereby preventing excessive ROS production and maintaining mitochondrial homeostasis [44]. Among the integrative pathways that mediate mitophagy, the most prominent molecular process is ubiquitin-dependent and is mediated by the phosphatase and tensin homolog (PTEN)-induced kinase (PINK1) and the E3 ubiquitin ligase Parkin [45]. Under normal physiological conditions, PINK1 is transported to the IMM, where it is cleaved by presenilin-associated rhomboid-like (PARL) protease and then released into the cytoplasm to be degraded by the ubiquitin–proteasome system [46]. When mitochondria are depolarized after being damaged, PINK1 cannot enter the IMM and steadily accumulates at the outer mitochondrial membrane (OMM), where it promotes the recruitment of Parkin to ubiquitinate several OMM proteins [47]. Adaptor proteins, such as p62, NDP52, OPTEN, and NBR1 bind to polyubiquitin chains and serve as bridges between dysfunctional mitochondria and nascent phagophores [48–50]. Alternatively, a ubiquitin-independent mode that involves selective receptors, such as BNIP3, NIX, and FUNDC1, can directly link mitochondria to the autophagic machinery by binding to LC3 [51–53](Fig. 2B).

Activation of mitophagy is supposed to be an adaptive response to lipid overload. Zhang *et al.* have observed that mitophagy is stimulated in the early stage of NAFLD in mice, as well as in hepatocytes after palmitic acid treatment. However, mitophagy is

impaired at late stage both *in vitro* and *in vivo* [54]. In contrast, Undamatla *et al.* have demonstrated that mitophagy gradually decreases as the disease progresses in another study. Reduced mitophagy is observed as early as one week after HFD feeding in mice liver [55]. These investigations have unveiled the complexity of NAFLD, in which the dynamics of mitophagy has been inconclusive. It should be noted that mitophagy is suppressed in patients with fatty liver disease [56], suggesting a failure of the adaptive response to lipid stress. A diet-induced murine model of NAFLD provided additional evidence for the compromised mitophagy as Parkin is significantly downregulated in the fatty liver [57]. Furthermore, Zhou *et al.* have demonstrated that a novel autophagy suppressor Mst1 contributes to the inhibition of Parkin through the AMPK pathway and that genetic ablation of Mst1 upregulates Parkin and restores mitophagy. Recently, Jin *et al.* described an alternative mechanism through which Parkin-dependent mitophagy is inhibited in NASH, which is an advanced form of NAFLD [58]. Disease progression induces degradation of the hepatocyte cytosolic protein Myc-interacting zinc-finger protein 1 (Miz1) and allows the release of PRDX6, which enables it to interact with Parkin, thereby inhibiting mitophagy. Similar to Parkin, BNIP3 is downregulated in palmitic acid-treated primary hepatocytes, providing another possible explanation for the blockage of mitophagy in NAFLD [59]. Further investigation has shown that the decrease of BNIP3 is attributed to the inhibition of Sirt 3 and the subsequent inactivation of the ERK-CREB signaling pathway. With the understanding that morphology dictates mitochondrial response to environmental stress and interaction with other organelles, a newly proposed Parkin-independent form of mitophagy, which is mediated by the p62-Keap1-Rbx1 pathway, is abrogated because of megamitochondria formation in fatty livers [60]. Intriguingly, Opa1 deficiency enables the mitochondria to switch from an immoderate fusion to a stationary equilibrium state, thereby mitophagy defects and liver damage are rescued. Predictably, restoration of mitophagy is a promising strategy to treat NAFLD. However, many additional issues remain to be addressed in understanding how mitophagy is suppressed and how it can be revived. For example, unveiling the key molecules that manipulate the integrated signaling pathway network involved in mitophagy inhibition may allow pharmacological compounds to restore this selective autophagy.

Reticulophagy

Reticulophagy, which is also termed as ER-phagy, is a selective form of autophagy through which damaged and excess subdomains are cleared to maintain homeostasis in the ER [61]. Similar to other selective autophagy, reticulophagy requires unique receptors to specifically recognize ER cargos. To date, six mammalian ER-resident proteins have been identified as selective reticulophagy receptors, namely FAM134B [62], SEC62 [63], RTN3L [64], CCPG1 [65], ATL3 [66], and TEX264 [67]. They all contain an LIR that directly interacts with LC3 and GABARAP. This interaction enables ER fragments to be engulfed by LC3-carrying autophagosomes, which then fuse with lysosomes for degradation (Fig. 3A). Lipotoxicity in NAFLD causes ER stress in hepatocytes [68]. Excessive and prolonged ER stress leads to the accumulation of misfolded proteins and overexpansion of ER membranes. Theoretically, in order to relieve ER stress, reticulophagy should be induced to eliminate damaged ER fragments and protein aggregates. A previous study has demonstrated the presence of reticulophagy in an *in vitro* model of NAFLD. Reticulophagy was found to be activated when HepG2 cells were treated with 400 μM of oleic acid for 8 h. This self-protective process may prevent apoptosis by activating the PI3K/AKT pathway, increasing BCL2 expression, and reducing lipotoxicity [69]. These findings suggest that reticulophagy plays a protective role in the early stage of NAFLD. Recently, we found that TEX264-mediated ER-phagy is activated to resolve ER stress in acetaminophen-induced liver injury [70]. However, the reticulophagy receptors involved in the pathogenesis of NAFLD and the underlying mechanisms for their regulation have not been reported. The use of phenobarbital in treating NAFLD provides some valuable clues [71]. This hepatic metabolic enzyme inducer was found to inhibit the formation of preneoplastic lesions in HFD-fed rats and correlate with increased expressions of the selective autophagy receptor p62 and the reticulophagy receptor FAM134B. Although the existing evidence implied that FAM134B-mediated reticulophagy is protective and a potential target for NAFLD treatment, loperamide-induced reticulophagy had been reported to be associated with autophagic cell death in glioblastoma cells. Additional studies are clearly needed to determine the explicit and specific role and the mechanism of reticulophagy in NAFLD.

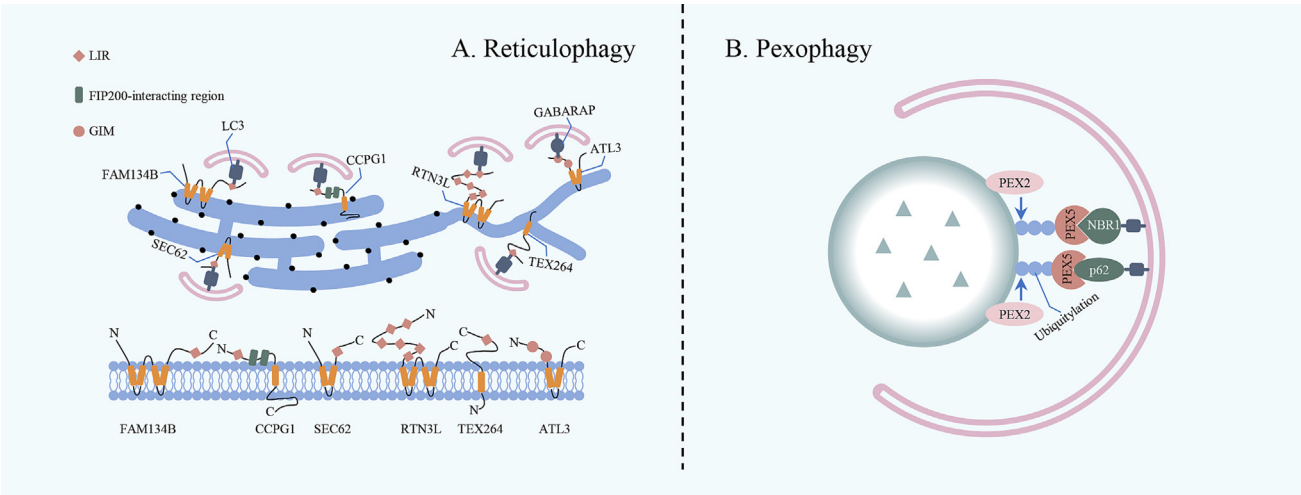

Fig. 3. Proposed models of key molecular events mediating reticulophagy and pexophagy in NAFLD. **(A)** Reticulophagy: In response to endoplasmic reticulum stress, selective autophagy receptors including FAM134B, CCPG1, SEC62, RTN3L, TEX264 and ATL3 bind to LC3/GABARAPs via their LC3-interacting regions (LIRs) or GABARAP-interacting motifs (GIMs) to initiate reticulophagy. FAM134B, CCPG1 and SEC62 locate at the rough endoplasmic reticulum, while RTN3L, TEX264 and ATL3 are all anchored to the smooth endoplasmic reticulum. **(B)** Pexophagy: PEX2 promotes the ubiquitination of PEX5. NBR1 or p62 subsequently binds to the ubiquitinated PEX5 and recruits the autophagosomes.

Pexophagy

Peroxisomes are extremely dynamic organelles that play a vital role in a variety of cellular catabolic and anabolic pathways, including β-oxidation of ultra-long chain fatty acids, synthesis of bile acid and ether phospholipid, and purine catabolic metabolism [72]. In addition, peroxisomes are also crucial for regulating cellular redox regulation because they can rapidly generate and eliminate ROS. Therefore, the biogenesis and degradation of peroxisomes must be finely tuned to prevent the dysregulation of lipid metabolism and oxidative stress. The primary degradation pathway of mammalian peroxisomes is pexophagy, through which peroxisomes are selectively enveloped and transported to lysosomes for digestion [73,74]. Specifically, PEX2, located in the peroxisomal membrane, promotes the ubiquitination of PEX5 [75]. NBR1 subsequently binds to the ubiquitinated PEX5 and recruits the autophagosomes. Although NBR1 acts as the dominant selective receptor in pexophagy [76], p62 may interact with NBR1 to facilitate the binding with the PEX5 and the recruitment of autophagy initiation machinery. In response to ROS, the kinase ataxia telangiectasia mutated (ATM) is triggered to phosphorylate PEX5, thus promoting its monoubiquitylation [77] (Fig. 3B).

At present, pexophagy is reported to be involved in the pathology of various diseases, including peroxisomal biogenesis disorders (PBDs) [78], neurodegenerative diseases [79], and aging [80]. Since peroxisomes are particularly abundant in the liver, and given the importance of peroxisomes in lipid metabolism, it would be of great interest to explore whether pexophagy plays a role in liver diseases. In the context of hypoxia-induced hepatic steatosis, Walter *et al.* observed the depletion of docosahexaenoic (DHA, $C_{22:6n3}$) and arachidonic acid (AA, $C_{20:4n6}$), which has also been reported in patients with NAFLD, and noted that the changes in lipid composition was partially due to the pexophagy induced by HIF-2α signaling [81]. Additionally, pexophagy is also induced in response to malnutrition, leading to the loss of peroxisomes and ultimately lipid accumulation in the liver [82]. Fenofibrate, one of the peroxisomal proliferator-actived receptor (PPAR) agonists, may inhibit pexophagy apart from promoting peroxisome biogenesis, thus alleviating malnutrition-induced liver steatosis. These preliminary discussions of how pexophagy is involved in hepatic steatosis raise the possibility that pexophagy might participate in the pathogenesis of NAFLD. Apparently more specific research is needed to clarify the role of pexophagy in NAFLD focusing on whether peroxisome-generated ROS or related lipid metabolism are involved.

Changes of the autophagic degradation pathway in NAFLD

Although specific organelles, such as the aforementioned LDs, mitochondria, ER, and peroxisomes, are selectively recognized and sequestered in autophagosomes, these are all delivered to lysosomes for degradation. Therefore, the late stage of autophagy, which is mediated by lysosomes, is particularly important for the overall autophagic flux. Initially, most studies monitored autophagic flux *in vitro* because of the limitations of detection methods. Tan *et al.* proposed that palmitic acid treatment significantly enhanced autophagic flux in MEFs and HepG2 cells, as evidenced by increased LC3-II levels and accumulation of GFP-LC3 puncta [83]. However, when primary hepatocytes were treated with palmitic acid for 24 h, the number of nonacidic autophagosomes significantly increased, but virtually no autolysosomes were produced; this indicated that the autophagic flux was reduced because of the blockage of lysosomal degradation [84]. Intriguingly, palmitic acid was shown to exert a time-dependent effect on autophagy in HepG2 cells by monitoring the changes in autophagic flux at different time points [85]. In Huh7 cells, González-Rodríguez *et al.* observed that after 800 μM palmitic acid treatment, p62 decreased at 8 h but increased at 24 h, which might be due to the blockage of lysosomal degradation [86]. Similar results on the dynamics of p62 were achieved in HL-7702 and HepG2 cells after treatment with 400 μM palmitic acid [87]. On the contrary, another study has shown that oleic acid but not palmitic acid, induced autophagy *in vitro* [88]. These confusing and controversial conclusions may be attributed to several factors, including the cell lines used, the type and concentration of fatty acids, and the time point selected in the studies. Overall, palmitic acid most likely induces autophagy in the early stage but impedes lysosomal degradation with long-term exposure. Furthermore, Liu *et al.* have established that in L02 cells, rapamycin as an autophagy activator alleviates palmitic acid-induced steatosis by promoting autophagy, whereas chloroquine as an autophagy inhibitor aggravates steatosis by interfering with lysosomal functions [89]. Based on the *in vitro* findings, *in vivo* studies are recommended to not solely focus on a particular stage of autophagy but to pay more attention to changes in autophagic flux during the development of NAFLD. A study using two murine models of NAFLD simultaneously found that after being fed an HFD or methionine-choline-deficient diet, there is a significant elevation in LC3-II protein levels, accompanied by p62 protein level decrease in the early stage and increase in the late stage [84]. Altogether, these results suggest that autophagic flux is initially activated to resist steatosis and prevent lipotoxicity, but is progressively blocked because of insufficient lysosomal degradation secondary to sustained metabolic stress. This means that NAFLD at the early onset can be treated by activating autophagy, and restoring the autophagic flux could be more effective in attenuating or preventing the progression of NAFLD at more severe stages.

Causes of impaired autophagic flux in NAFLD

The aforementioned findings raise a question on autophagic flux: what cause the obstruction of lysosomal degradation in NAFLD? Several possible explanations have been proposed based on relevant evidence.

Impairment of autophagic-lysosomal fusion

Lipotoxic stress has long been recognized to alter the lipid composition and affect the rigidity and fluidity of membranes, thereby perturbing the biological function of membranous organelles. Compared with animals on a normal diet, those who fed an HFD were found to have reduced autophagosome-lysosome fusion by up to 70 % [90]. To determine the autophagosome-lysosome fusion dysfunction in NAFLD, *in vitro* experiments were performed using palmitic acid in HepG2 cells [91]. Using anti-LC3-II and anti-LAMP1 antibodies for visualization, there was practically no interaction between autophagosomes and lysosomes, respectively, in the cells. In addition, measurement of autophagic flux using mCherry-GFP-LC3 indicated that few autolysosomes were formed after palmitic acid treatment. These mutually corroborating *in vitro* and *in vivo* findings are sufficient to demonstrate that lipotoxicity suppresses autophagic flux, at least partially by blocking the fusion of autophagosomes and lysosomes. Several studies have attempted to unveil the molecular mechanisms underlying the compromise of this fusion process. Rubicon, which is a protein localized at the lysosomes, has been shown to be involved in the inhibition of autophagosome-lysosome fusion in NAFLD [92]. Miyagawa *et al.* described that another possible mechanism of fusion impairment in hepatocytes is disruption of ER homeostasis by lipid overload, resulting in ER stress, which is associated with the blockage of autophagy at the late stage [93].

Perturbation of normal lysosomal function

The structural integrity and physiological function of the lysosome are are fundamental to the degradation process of autophagy. However, many studies have reported that lipotoxicity in NAFLD causes lysosomal dysfunction, including disturbed lysosomal acidification [94], lysosomal membrane permeabilization (LMP) [95], and decreased lysosome hydrolase activity [96,97]. Additional studies have clarified the underlying mechanisms.

Lysosomes contain a variety of hydrolytic enzymes, such as proteases, glycosidases, and lipases, which mediate catabolic function. To ensure the activity of these enzymes, which are crucial for lysosomal function and autophagic flux, lysosomes must maintain an acidic environment with pH of 4.5–5.0 [98]. Lysosomal acidification is primarily established by vacuolar H^+-ATPase (V-ATPase), which is an ATP-driven proton pump. In a murine model of steatohepatitis (i.e., obese KKAy mice), hepatic steatosis-induced downregulation of lysosomal proton pump V-ATPase was demonstrated to be likely responsible for defective autophagic acidification [99]. Furthermore, the decrease of V-ATPase may be attributed to the suppression of retinoic acid-related orphan receptor α, which is one of its transcriptional regulators and was also found to be dramatically downregulated in HFD-fed mice and patients with hepatitis [100]. Wang *et al.* have provided an additional explanation that ER stress-induced asparagine synthetase inhibits lysosomal acidification [101].

LMP is a process in which cathepsin and hydrolase leak from the lysosome secondary to membrane disruption, resulting in lysosomal dysfunction and affecting autophagic flux. Exposure to long-chain FFAs triggers LMP in mouse and human hepatocytes, leading to the release of the lysosomal cysteine protease cathepsin B, which is an apoptosis-specific mediator, into the cytoplasm and inducing cell damage. In addition, mitochondrial dysfunction and ROS production are downstream of LAM that is induced by saturated long-chain FFAs [102], which in turn may impair autophagy. It should be noted that lysosomes and mitochondria interact with each other, and this relationship between them is not unidirectional. Bax has been identified as a crucial mechanistic mediator of LMP in hepatocytes. We and other researchers have observed that genetic or pharmacological blockade of Bax in liver cells inhibited FFAs-induced LMP and reduced subsequent apoptosis [103,104]. In addition, acid sphingomyelinase, which is required for TNF-induced apoptosis, has been reported to promote HFD-induced LMP, and contribute to hepatic steatosis and lipotoxicity [105].

Approximately 60 enzymes are enclosed in lysosomes, of which cathepsins represent the predominant hydrolases for autophagic degradation. In the liver of mice and patients with NAFLD, there is growing evidence that the expression or activity of lysosomal hydrolases such as cathepsin B, cathepsin D, cathepsin L, and lysosomal acid lipase are suppressed [94,97,106]. Given their primary role in breaking down cellular components derived from autophagosomes, insufficient lysosomal hydrolases will inevitably dampen lysosome-mediated autophagic proteolysis process. However, only few investigations have described the precise molecular mechanisms underlying the suppression of these lysosomal hydrolases.

Suppression of lysosomal biogenesis

During nutritional starvation, transcription factor EB (TFEB) is transported to the nucleus and binds to the gene promoter regions that contain coordinated lysosome expression and regulation elements, thereby rapidly inducing the expression of genes involved in lysosomal biogenesis and autophagy [107,108]. Likewise, the predominant regulator of lysosomal biogenesis in liver diseases is TFEB, which is unfortunately suppressed in alcohol-induced liver injury and NAFLD [109,110], suggesting that the lysosomal biogenesis may be impaired. The reduction of Lamp1-positive and GFP-LC3 puncta in alcohol-exposed hepatocytes provides additional direct evidence for a deficiency in lysosomal biogenesis. However, thus far, no direct evidence has demonstrated that lysosome numbers decrease in response to overnutrition, although TFEB activation through its agonists is protective against diet-induced steatosis in mice [111]. In fact, TFEB transcriptionally activates genes that regulate mitochondrial function and peroxisome biogenesis; therefore, a definitive conclusion that lysosomal biogenesis is impaired in NAFLD cannot be drawn on the basis of reduced TFEB nuclear translocation alone. Overall, defective lysosomal biogenesis may be responsible for the blocked autophagic flux, and more specific manipulations of lysosomal biogenesis are required to establish a causal relationship.

Therapeutic strategies against NAFLD based on selective autophagy

As we have discussed in this review, selective autophagy is the predominant route by which aberrant organelles are cleared, and thus cells are able to limit intracellular damage and maintain homeostasis in response to lipid overload. However, in the pathogenesis of NAFLD, the late steps in the autophagic flux are disrupted by lipids due to its detrimental effect on autophagosomes and lysosomes. Therefore, there are thus far two primary strategies for NAFLD treatment based on selective autophagy machinery: promoting the early molecule events in selective autophagy, and restoring the autophagic flux by targeting the late phase.

With the aforementioned concepts in mind, we summarize the therapeutic approaches to stimulate selective autophagy for NAFLD (Table 1). Physical exercise and diet intervention are in the frontline for NAFLD patient management. The high effectiveness of these lifestyle interventions may be partially attributed to their ability to promote lipophagy [112,113]. Exercise not only facilitates lipophagy via activation of AMPK, but also activates PINK1/Parkin-mediated mitophagy to eliminate the accumulated nonfunctional mitochondria [114]. Besides, various medications or natural products can also serve the same purpose. Quercetin, a naturally occurring flavonoid, ameliorates HFD-induced NAFLD by promoting lipophagy via the IRE1α/XBP1s pathway and activating frataxin-mediated PINK1/Parkin-dependent mitophagy [115, 116]. Fenofibrate [117], ajugol [118], phillygenin [119], nobiletin [120], formononetin [121], and metformin [122] (Table 1) have all been reported to alleviate liver steatosis by promoting TFEB-mediated autophagy-lysosomal pathway and lipophagy, and may become potential candidates for the prevention and treatment of NAFLD. Liu *et al.* have established that honokiol, a lignan from the plants of Magnolia genus, alleviates lipotoxicity *in vitro* and *in vivo* via activating SIRT3-AMPK-lipophagy axis [123]. Like fenofibrate, stevioside and sulfated glucuronomannan hexasaccharide G6S1 promote lipophagy via PPARα pathway to limit liver steatosis. In addition to lipophagy, many compounds such as liraglutide [124], cyanidin-3-O-glucoside [125], etc. (Table 1) have been demonstrated to stimulate mitophagy and have shown promise in treating NAFLD.

The biggest issue for selective autophagy in NAFLD is the inability of lysosomes to appropriately degrade damaged or excess organelles. Herein, we outline currently available interventions targeting lysosomes for the treatment of NAFLD. First, rescuing the disrupted autophagosome-lysosome fusion. Calcium channel blockers such as verapamil, which is commonly used in clinical practice to treat diseases of the heart and vascular system, have been found to be benificial in obesity-related metabolic diseases [91]. Interestingly, pharmacological inhibition of calcium channels using the FDA-approved drug vera-

Table 1
Therapeutic means of activating selective autophagy in NAFLD.

Treatment	Model	Dose	Type of selective autophagy	Related mechanism
Exercise	45 % HFD for SD rats [112]	60 min/day	Lipophagy	AMPK/ULK1
	45 % HFD for mice [113]			
	60 % HFD for mice [142]	Moderate treadmill running		
	71 % HFD for SD rats [114]	60 min/day	Mitophagy	PINK1/ Parkin
Quercetin	30 % HFD for SD rats	100 mg/kg	Lipophagy	IRE1α/XBP1s
	1 mM FFA for HepG2 [115]	100 μM		
	750 μM FFA for AML12 [143]	10 μM		AMPK
	MCD diet for mice	20, 80 mg/kg	Mitophagy	AMPK/PINK1/Parkin
	600 μM OA for HepG2 [144]	100 μM		
	60 % HFD for mice	100 mg/kg	Mitophagy	Frataxin/PINK1/Parkin
	2 mM FFAs for HepG2 [116]	100 μM		
Fenofibrate	60 % HFD for mice	100 mg/kg	Lipophagy	PPARα/TFEB
	0.5 mM OA for HepG2 cells [117]	100 μM		
Ajugol	60 % HFD for C57BL/6 mice [118]	50 mg/kg	Lipophagy	TFEB
Phillygenin	HFD for mice	12.5, 25, 50 mg/kg	Lipophagy	TFEB
	0.4 mM PA for AML12 or hepatocytes [119]	10, 20 μM		
Nobiletin	HFD fed ApoE$^{-/-}$ mice [120]	50, 100, 200 mg/kg	Lipophagy	TFEB
Formononetin	60 % HFD for mice	100 mg/kg/day for mice	Lipophagy	TFEB
	1 mM FFAs for HepG2 or hepatocytes [121]	20 μM for cells		
Metformin	60 % HFD or MCD diet for mice	200 mg/kg for mice	Lipophagy	TTP/Rheb/TFEB
	200 μM OA for AML12 or hepatocytes [122]	2 mM for cells		
Zinc	Yellow catfish [145]	8.83, 19.20, and 146.65 mg/kg	Lipophagy	Zn^{2+}/MTF-1/PPARα and Ca^{2+}/CaMKKβ/AMPK
Honokiol	Choline-deficient HFD for mice	2.5, 10 mg/kg for mice	Lipophagy	SIRT3-AMPK
	750 μM FFAs for AML12 cells [123]	2.5, 5, 10 μM for cells		
Stevioside	db/db mice	40 mg/kg for mice	Lipophagy	PPARα
	1 mM FFAs for HepG2 cells [146]	0–100 μM for cells		
G6S1	100 μM OA for AML12 cells [147]	100, 400 μg/mL for cells	Lipophagy	PPARα
Liraglutide	0.4 mM PA for HepG2 cells [124]	50, 100, 200, and 500 nM	Mitophagy	PINK1/Parkin
	60 % HFD for mice [148]	150 mg/kg for mice		
Cyanidin-3-O-glucoside	60 % HFD for mice	2 g/kg for mice	Mitophagy	PINK1/Parkin
	400 μM PA for AML12 and HepG2 cells [125]	100 μM for cells		
Melatonin	60 % HFD for mice	20 mg/kg for mice	Mitophagy	Bnip3
	75 μM PA for primary hepatocytes [149]	100 μM for cells		
	58.4 % HFD for mice [150]	10 mg/kg for mice		
Hydroxytyrosol	16 % HFD for spotted seabass juveniles	200 mg/kg in diet for fish	Mitophagy	AMPK/PINK1
	0.5 mM FFAs for zebrafish liver cell line [151]	50 μM for cells		
Akebia saponin D	200 μM OA for BRL cells [152]	100 μM	Mitophagy	Bnip3
Corilagin	60 % HFD for mice	20 mg/kg for mice	Mitophagy	Parkin
	200 μM FFAs for AML12 cells [153]	10, 20 μM for cells		
Nicotinamide adenine	60 % HFD or MCD diet for mice [154]	400 mg/kg	Mitophagy	SIRT2/Fndc5
Pyrvinium pamoate	HFD for SD rats [155]	60 μg/kg	Mitophagy	PINK1/ Parkin

pamil restores membrane fusion between the autophagosome and lysosome not only in HepG2 cells but also in mouse livers, thereby reducing the accumulation of protein inclusions and lipid droplets, and improving the pathologies associated with fatty liver, such as inflammation and insulin resistance [126]. In addition, several plant-derived compounds have been shown to ameliorate NAFLD by reversing the dysfunction of autophagosome-lysosome fusion. Akebia Saponin D, a typical bioactive triterpenoid saponin isolated from the rhizome of Dipsacus asper Wall, has been found to increase autophagosome-lysosome fusion in mice fed HFD, thereby reducing hepatic steatosis [127]. Besides, psoralen, a natural flavonoid derived from Cullen corylifolium (L.) Medik (syn. Psoralea corylifolia L), has been shown to improve insulin resistance and restore lipid metabolism homeostasis in the context of NAFLD, and that is achieved by promoting autophagic initiation and autophagosome-lysosome fusion [128]. Formononetin and ajugol have also been reported to promote the fusion of autophagosome and lysosome, restore lipophagy and reduce lipid accumulation [118,121]. Second, restoring lysosomal functions. Several natural products, such as polydatin [129], baicalein [130], epigallocatechin-3-gallate [131], malvidin-3-O-glucoside [132], peonidin-3-O-glucoside [133], and resveratrol [134] have been reported to serve this goal, thereby rescuing impaired autophagic flux and reducing lipid accumulation in NAFLD. Particularly inspiring is that Zeng *et al.* synthesized a novel biodegradable nanoparticle that targets lysosomes, where the nanoparticles are activated and enhance the function of lysosomes. By re-acidifying lysosomes, the acid-activated nanoparticles restore autophagy and metabolic dysfunction in NAFLD [135]. Intriguingly, promoting lysosomal proteolysis and acidification has also been demonstrated to be one of the mechanisms by which physical exercise mitigates hepatic steatosis, which is associated with down-regulation of fatty acid-binding protein 1 (FABP1) signaling pathway [136]. Finally, promoting lysosomal biogenesis. Numerous natural products, such as nuciferine [137], procyanidin B2 [138], and catalpol [139] have been demonstrated to promote nuclear translocation of TFEB, a primary regulator of lysosomal biogenesis, thus alleviating NAFLD. This process provides a sufficient amount of nascent lysosomes to avoid exhausting degradative organelle by lipotoxicity-induced excess autophagosomes. However, the protective effect of TFEB in NAFLD may be not only attributed to lysosomal biogenesis, as peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) can be transcriptionally activated by TFEB, leading to upregulation of lipid degradation, fatty acid oxidation, and downregulation of lipid biosynthesis [140]. In addition, TFEB upregulates the expression of FGF21 by binding to the

CLEAR motif within its gene promoter, through which TFEB exerts protection effect against NAFLD [141].

Concluding remarks

In summary, selective autophagy is an essential pathway for the elimination of specific damaged organelles that emerge during the progression of NAFLD and the deregulation of this process is involved in the pathogenesis of this disease. Therefore, strategies that target selective autophagy have shown great potential in treating NAFLD. Although the therapeutic efficacy of most interventions is unquestionable, more selective activators that target different types of autophagy are likely to provide greater benefits to patients with NAFLD. Because autophagy has varied and sometimes opposing effects on various cell types, selectivity to particular liver cells should also be considered. On the other hand, because of the complexity of the pathogenesis of NAFLD, drug combinations that include initiating autophagy and restoring the blocked degradative process may be an efficient approach to treat NAFLD.

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None declared.

CRediT Author contribution statement

Suwei Jin: Conceptualization, Visualization, Writing-original draft. **Yujia Li:** Writing-review & editing. **Tianji Xia:** Validation. **Yongguang Liu:** Validation, Visualization. **Shanshan Zhang:** Visualization. **Hongbo Hu:** Writing-review & editing. **Qi Chang:** Funding acquisition, Writing-review & editing. **Mingzhu Yan:** Funding acquisition, Conceptualization, Writing-original draft, Writing-review & editing; Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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