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Review

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Rescuing lysosomal/autophagic defects via nanoapproach: implications for lysosomal/autophagic defect-related diseases

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Abstract: The dysfunction of the lysosome and autophagy-lysosome system serves as a driving force for neurodegenerative diseases, metabolic disorders, inflammatory conditions, and other related diseases, closely influencing their onset and progression. Therefore, restoring the function of the lysosome or autophagy-lysosome system has become an increasingly crucial therapeutic strategy in disease management. In this review, we will introduce the lysosomal biogenesis, structure, and function, as well as the biological process of the autophagy-lysosome system. Various diseases closely associated with lysosomal/autophagic dysfunction are also reviewed, emphasizing the significance of targeting the function of the lysosome or autophagy-lysosome system in disease treatment. Finally, we focus on engineered nanomaterials that have the capabilities to restore the function of the lysosome or autophagy-lysosome system, and summarize different strategies and methods for achieving this goal. This review aims to elucidate the latest progress in the field of nanomedicine for lysosomal/autophagic defect-related diseases and inspire the development of innovative and clinically valuable nanomedicines.

Key words: Lysosome; Autophagy; Lysosomal/autophagic disfunction; Acidic nanoparticle; Transcription factor EB (TFEB); Dementia; Alzheimer's disease

1 Introduction

Lysosomes, as the primary digestive compartments within cells, consist of an acidic lumen and lysosomal membranes formed by phospholipid bilayers. The acidic compartment of lysosomes contains approximately 60 acidic hydrolytic enzymes competent in clearing complex carbohydrates, large proteins, lipids, and other molecules (Gros and Muller, 2023; Settembre and Perera, 2024). The acidic environment within the lysosomal compartment is helpful for ensuring the optimal functioning of digestive enzymes and other chemicals involved in breaking down lysosomal targets, and promoting the digestion and decomposition of unnecessary cellular components, cell fragments, or foreign substances. Therefore, maintaining the acidic pH within lysosomes is crucial for their function and cellular protection. With further research, lysosomes are not only a degradative factory but are also important regulators for nutrient sensing, receptor recycling and/or modulation, exocytosis, cholesterol homeostasis, and cell death (Ballabio and Bonifacino, 2020; Holland et al., 2020; Settembre and Perera, 2024).

Autophagy, a highly conserved lysosome-dependent degradative process in eukaryotic cells, degrades intracellular excess or impaired organelles, misfolded proteins, nucleic acids, lipids, and invasive pathogenic microorganisms to maintain normal cellular biological functions; recycles the energy and substances when there are metabolic nutritional deficiencies such as starvation and hypoxia; and reconstructs the substances needed to maintain the basic life activities of

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cells (Mizushima and Komatsu, 2011; Levine and Kroemer, 2019; Aman et al., 2021). Therefore, the autophagic process is commonly regarded as a stress response mechanism that promotes the survival of eukaryotes.

Dysfunction of lysosomes and autophagy-lysosome systems often contributes to the occurrence and progression of various diseases. Dysregulation of lysosomes and/or autophagy-lysosome systems is closely related to the onset and development of neurodegenerative diseases (Schützmann et al., 2021; Griffey and Yamamoto, 2022; Lee et al., 2022), metabolic disorders (Zeng et al., 2023), and inflammatory conditions (Mareninova et al., 2009). Therefore, restoring lysosomal and autophagy-lysosome system function has become an increasingly important therapeutic strategy for disease management.

This review highlights the intervention of various nanomaterials in lysosomal and autophagic/lysosomal defect-related diseases by restoring lysosomal acidification and autophagy flux. First, we describe lysosomal biogenesis, structure, and functions, as well as the autophagic process. Second, we review various diseases associated with lysosomal/autophagic dysfunction. Finally, we focus on engineered nanomaterials capable of regulating the acidity and degradation capacity of lysosomes and restoring autophagy flux. This review summarizes different strategies and methods for regulating the acidity and degradation capacity of lysosomes and restoring autophagy flux, providing an important reference for the development of new methods of disease intervention and clinical translation applications.

2 Lysosome/autophagy-lysosome pathway

2.1 Lysosomal biogenesis, structure, and function

Lysosomes are heterogeneous and dynamic organelles with a single-layer membrane structure, meaning that the positions, morphologies, sizes, enzyme contents, and substrates of different lysosomes can vary significantly (Zhao et al., 2021). A lysosome contains hundreds of acidic hydrolases, including proteases, nucleases, glycosidases, and phosphatases, some of which are integrated into the lysosomal membrane and influence the transportation of biological macromolecules and ions (Bagshaw et al., 2005; Chapel et al., 2013; Braulke et al., 2024). Lysosomal biogenesis requires the coordination of the biosynthesis of lysosomal proteins and endosome-lysosomal trafficking. The transcriptional regulation of transcription factor EB (TFEB), as well as the integration of endocytic and biosynthetic cellular pathways, can affect the biogenesis of lysosomes (Shimobayashi and Hall, 2014). Since lysosomal activity is critical for maintaining cellular homeostasis, lysosomal biogenesis must be rigorously controlled. When cells are in a non-starved state, the mechanistic target of rapamycin (mTOR) complex 1 (mTORC1), a major regulatory factor for cell growth, would be activated on the lysosomal membrane (Shimobayashi and Hall, 2014). Activated mTORC1 would further suppress TFEB and prohibit its nuclear transport, thereby hindering lysosome biogenesis (Sardiello et al., 2009). When cells are in a low-nutrient state, mTORC1 would be repressed, subsequently leading to the release of TFEB (Settembre et al., 2013; Hämälistö and Jäättelä, 2016). Dephosphorylated TFEB would be transported to the nucleus and further participate in lysosome biogenesis and the transcription of autophagy genes (Martina et al., 2012). Lysosome-related proteins are translated in the rough endoplasmic reticulum and go through two distinct pathways for lysosomal development: one involves directly targeting the trans-Golgi network (TGN) endosomal network, or indirectly targeting the transport of proteins to TGN through the constitutive secretion pathway; the other involves endocytosis (Saftig and Klumperman, 2009). Once inside endosomes, cargo can be transported to lysosomes through both kiss-and-run mechanisms and fusion pathways. Lysosomal membranes contain membrane-integrated proteins with varying acidity and high glycosylation, including lysosomal-associated membrane proteins 1 (LAMP1/CD107a) and 2 (LAMP2/CD107b) (Howe et al., 1988; Kornfeld and Mellman, 1989). LAMPs play a crucial role in maintaining lysosomal homeostasis, motility, and membrane integrity (Saftig and Klumperman, 2009; Boya, 2012), which also play the crucial roles in autophagic pathway-related lysosomal fusion (Eskelinen, 2006). LAMPs can be located in lysosomes through the aforementioned direct and indirect pathways during lysosomal biogenesis (Howe et al., 1988; Janvier and Bonifacino, 2005). The type of LAMP and intracellular conditions determine its exit position from the TGN, which in turn determines the

transport pathway of LAMPs (Howe et al., 1988; Carlsson and Fukuda, 1992; Janvier and Bonifacino, 2005). Hydrolases, such as cathepsin B/D, can be shipped from early endosomes to lysosomes by virtue of direct or indirect pathways, which, when transported via the direct pathway, can form mannose-6-phosphoprotein through glycosylation and phosphorylation, and bind to mannose-6-ahosphate receptors (M6PRs). In the acidic microenvironment, M6PRs dissociate from the enzymes and return to TGN for recycling (Howe et al., 1988; Mari et al., 2008). Lysosomal hydrolases acquire mannose-6-phosphate tags upon passing through the Golgi complex and bind to M6PRs located in TGN, facilitating their direct transport to the endosome network (Howe et al., 1988). Therefore, lysosomal hydrolases are primarily localized within subcellular lysosomal and endosomal compartments, which could be used as an indicator of lysosomal function.

2.2 Autophagy-lysosome pathway

The autophagic process mediates the clearance of excess or aging cellular components, damaged proteins, lipids, nucleic acids, and the intruding pathogenic microorganisms within the cells to sustain normal cellular biological functions (Dikic and Elazar, 2018). Especially in the case of metabolic nutritional deficiencies, such as starvation and hypoxia, cells can recycle the energy and substances produced by autophagy degradation and reconstruct the substances necessary to maintain their basic life activities. According to the routes of delivery of intracellular substrates to lysosomes, autophagy is generally categorized as macroautophagy, microautophagy, or chaperone-mediated autophagy (CMA) (Mizushima and Komatsu, 2011; Parzych and Klionsky, 2014). Microautophagy refers to a lysosome-dependent degradative process, during which cytoplasmic contents enter the lysosome compartment by an invagination or deformation of the lysosomal membrane and are subsequently degraded by lysosomes (Fig. 1a). The gradual and continuous turnover of cytoplasmic proteins depends on microautophagy, even under resting conditions. CMA is a transient and secondary response associated with autophagy. Almost all vertebrate cell lysosomal membranes possess LAMP type 2A (LAMP-2A), capable of building a hexameric channel. Additionally, LAMP-2A could specifically identify and bind to proteins carrying the

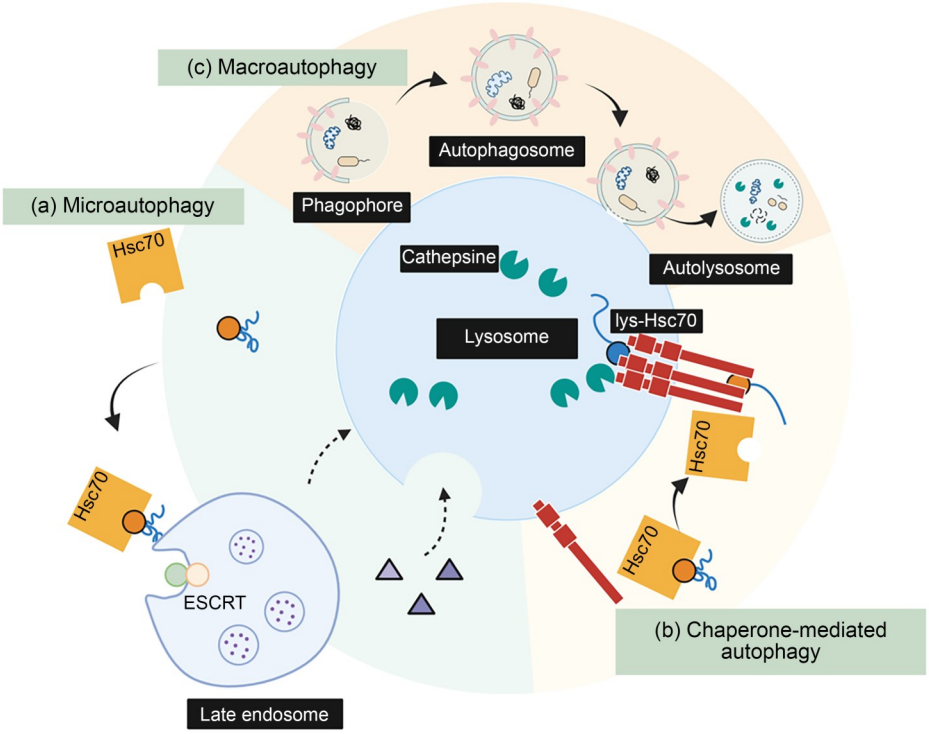

Fig. 1 Routes of delivery of intracellular substrates to lysosomes. Microautophagy (a), chaperone-mediated autophagy (b), and macroautophagy (c). Created by BioRender.com. Hsc70: heat-shock cognate protein 70 kDa; lys-Hsc70: lysosome-associated Hsc70; ESCRT: endosomal sorting complex required for transport.

exposed pentapeptide motif (KFERQ). With the assistance of heat-shock cognate protein 70 kDa (Hsc70), proteins containing the KFERQ-like motif are directly translocated into the lysosomal compartment and subsequently cleared by lysosomal proteases (Mizushima and Komatsu, 2011; Parzych and Klionsky, 2014; Lescat et al., 2018) (Fig. 1b). Macroautophagy (hereafter, denoted as autophagy) is the most typical and widespread autophagic process (Parzych and Klionsky, 2014), including the formation and maturation of double-membrane autophagosomes, the autophagosome-lysosome fusion, and the degradation and recycling of cytoplasmic components (Rubinsztein et al., 2007; Mak et al., 2010) (Fig. 1c). The main distinction between macroautophagy, CMA, and microautophagy is characterized by the formation of double-membrane autophagosomes. Various types of substances, such as impaired organelles, misfolded proteins, or invasive pathogenic microorganisms, could be encapsulated into autophagosomes and digested upon the fusion between autophagosomes and lysosomes to realize matter and energy recycling, as well as maintain the cellular homeostasis (Martens and Fracchiolla, 2020).

3 Lysosomal/autophagic dysfunction-related diseases

Despite various factors influencing the pathogenic mechanisms of different diseases, numerous studies have suggested that lysosomal/autophagic-lysosomal defects play crucial roles in the onset and progression of neurodegenerative diseases, natural aging, inflammation-related diseases, and non-alcoholic fatty liver disease (NAFLD) (Aman et al., 2021) (Fig. 2). Reasonable regulation and intervention of lysosome/autophagy-lysosome pathway (ALP) hold great potential for effective disease intervention. The lysosomal acidification defects and the failure of lysosome-organelle fusion could cause damage to endocytosis, the autophagic degradative process, and the synthesis and transport of biomacromolecules. The activity of other organelles, for example, the mitochondria, is affected by lysosomal acidification dysfunction, which will increase the production of reactive oxygen species (ROS) and inflammatory cytokines, leading to inflammatory diseases, cancer, and infectious diseases.

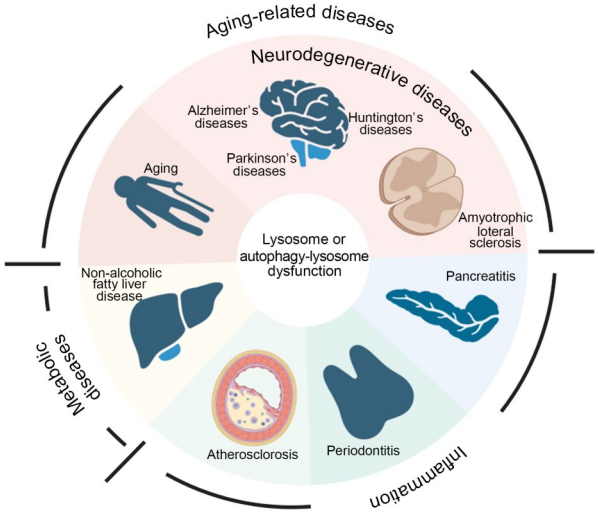

Fig. 2 Various diseases related to lysosomal/autophagic defects. Created by BioRender.com.

3.1 Neurodegenerative diseases

3.1.1 Alzheimer's disease

Alzheimer's disease (AD) has a relatively high incidence rate and is a major cause of dementia in the elderly (Nowell et al., 2023). The main hallmark of AD is the aggregation of misfolded proteins in neuronal cells, including β-amyloid (Aβ) peptide and microtubule-associated protein tau (MAPT) (Davoody et al., 2024), which can cause neuroinflammation and neuronal death (Zhang et al., 2022). Therefore, a promising therapeutic strategy for AD is to eliminate Aβ and MAPT aggregates (Lee and Nixon, 2022; Lee et al., 2022; Xie et al., 2022; Iyaswamy et al., 2023; Zhang XW et al., 2023). Many studies have reported that mitochondrial and lysosomal dysfunction could be a response to the Aβ and tau deposition in AD, and conversely, the accumulation of damaged lysosomes and mitochondria in the brain could promote the onset and development of AD (Fang et al., 2019; Xu et al., 2022; Veverová et al., 2024). Thus, enhancing autophagic or mitophagic activity could contribute to the clearance of Aβ and tau and neuronal protection effects. Wang et al. (2023) studied the interactions between pituitary adenylate cyclase-activating polypeptide (PACAP) and autophagy in AD. They found that PACAP could restore autophagy, reduce amounts of Aβ and tau deposition, and subsequently improve cognitive function in AD. Xu et al. (2022) reported that the delivery efficiency of rapamycin to neurons

in AD could be enhanced by ROS-responsive micelles, thereby improving autophagic flux and restoring neuronal proteostasis. Microglia could promote the clearance of Aβ and tau plaque in AD and maintain the cognitive function of neurons (Litwiniuk et al., 2023). The literature indicates that up-regulating the expression of autophagy-related proteins, sequestosome 1 (SQSTM1/p62) and microtubule-associated protein 1 light chain 3 (MAP1LC3/LC3), in ALP could activate microglial cell autophagy in AD and restore the phagocytic and clearance function of the Aβ and tau aggregates (Choi et al., 2023; Zhang XW et al., 2023), suggesting that regulating autophagy might be a promising strategy to improve cognitive function in AD. Additionally, the literature has also shown that the deficiency in lysosomal acidification function in AD mouse models and the impairment of ALP degradation could lead to autophagic accumulation of Aβ, resulting in age-related plaques in neurons (Lee et al., 2022; Veverová et al., 2024). Therefore, the lysosome and/or autophagy-lysosome are crucial for the pathogenesis of AD, and methods to regulate autophagy and restore autophagic flux are deemed necessary to improve the neuronal proteostasis of AD.

3.1.2 Parkinson's disease

Parkinson's disease (PD) has increasing prevalence with age and is related to environmental toxins and genetic mutations (Ben-Shlomo et al., 2024). The major hallmarks of PD are the loss of dopaminergic neurons and the presence of abnormal protein aggregates within Lewy bodies in neurons of the substantia nigra compacta (Morris et al., 2024). Studies have revealed that lysosomal dysfunction, autophagic impairment, and mitochondrial dysfunction act as the fundamental aetiopathogenesis of PD (Wallings et al., 2019; Prieto and Cotman, 2022; Payne et al., 2024). Mutant α-synuclein (α-syn) aggregates could lead to the onset and development of AD, and could be degraded by lysosomes during ALP (Calabresi et al., 2023; Lee et al., 2023). Aging, genetic predisposition, and environmental exposures may contribute to the dysfunction of autophagy and lysosomes, resulting in the aggregation of α-syn (Mamais et al., 2023). It is also suggested that the accumulation of α-syn could disrupt autophagy and induce lysosomal dysfunction, which is harmful to neuronal survival (Tu et al., 2021), and the number of lysosomes decreases in dopamine neurons in the substantia nigra compacta of PD patients (Dehay et al., 2010). Therefore, there is a correlation between lysosome and/or autophagy dysfunction and PD pathogenesis, and enhancing autophagy or restoring autophagic/lysosomal function to remove mutant α-syn may represent a novel therapeutic approach for PD (Guo et al., 2021; Zhang K et al., 2021; Zhu et al., 2023).

3.1.3 Huntington's disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder resulting from a mutation in the huntingtin (*HTT*) gene on chromosome 4 (McColgan and Tabrizi, 2018; Pan and Feigin, 2021; Devadiga and Bharate, 2022). The manifestations of HD primarily include progressive motor dysfunction, cognitive dysfunction, and mental disorders (Devadiga and Bharate, 2022). In normal individuals, the HTT protein typically has fewer than 36 CAG repeat sequences, and the *HTT* gene contains fewer than 36 glutamine residues in the polyglutamine repeat sequence. However, the HTT protein contains more than 36 glutamine residues, prone to abnormal conformation and misfolding of the mutant HTT (mHTT) in HD patients (Ayyildiz et al., 2023; Yan et al., 2023). The accumulation of the mHTT proteins in the central nervous system increases with aging, leading to neuronal damage and eventual cell death, contributing to the progression of HD (Li et al., 2019; Ardan et al., 2020; Krach et al., 2022). It is suggested that the accumulation of mHTT leads to lysosomal and autophagic dysfunction (Zhang ZQ et al., 2021). However, there are also studies indicating that the ineffective clearance of mHTT may be due to its inability to be effectively delivered to autophagosomes. It has been observed that the number of autophagosomes in the neurons of HD patients keeps increasing and the autophagic flux maintains appropriate or even higher levels (Kegel et al., 2000; Martinez-Vicente et al., 2010). Additionally, the aggregation of mHTT and impaired organelles is inadequately sequestered into autophagosomes, resulting in their buildup in the cytoplasm and ensuing cytotoxicity (Martinez-Vicente et al., 2010).

3.1.4 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease caused by the lower motor neurons in the spinal cord ventral horn, cerebral cortex,

and brainstem nuclei (Ilieva et al., 2023). ALS has two types, with sporadic cases accounting for 90% of cases and familial cases accounting for the remaining 10% (Feldman et al., 2022). Mutations in the superoxide dismutase 1 (*SOD1*) gene affect approximately 20% of familial ALS patients. *SOD1* mutants are susceptible to conformational changes, resulting in abnormal aggregation of proteins, which may be the cause of ALS disease (Bruijn et al., 1998; Chattopadhyay and Valentine, 2009; Kaur et al., 2016). Studies investigating the pathogenic mechanisms of *SOD1* mutants in ALS patients have revealed the presence of aggregated inclusions in both familial ALS patients and mouse models injected with the human *SOD1* transgene containing a glycine-to-alanine substitution at position 93 (dal Canto and Gurney, 1995). Additionally, spinal cord samples from ALS patients with *SOD1* mutations show lower autophagic capacity and higher levels of *SOD1* aggregation (Piras et al., 2016). *SOD1* aggregates could escape normal degradation processes and exert toxicity to autophagy, resulting in dysfunctional autophagy (Robberecht and Philips, 2013). Chen et al. (2012) experimentally validated that the dysregulation of autophagic function was related to the presence of protein products of ALS-related genes. Therefore, utilizing autophagy to eliminate toxic *SOD1* aggregates holds significant potential for ALS treatment (Liu et al., 2022).

3.2 Non-alcoholic fatty liver disease

NAFLD is a liver manifestation of metabolic syndrome, with lower levels of autophagy in liver cells (Lebeaupin et al., 2018). The patients with severe steatosis show significant accumulation of autophagy substrate protein SQSTM1/p62 (Fukuo et al., 2014; Kashima et al., 2014). The mechanisms of autophagic impairment in NAFLD are as follows: (1) increased expression of calcium-dependent protease calpain II induced by obesity leading to autophagy-related 7 (ATG7) degradation and autophagic defects (Yang et al., 2010); (2) over-activation of the autophagy inhibitor mTOR in the liver; (3) hyperinsulinemia (Liu et al., 2009); (4) lysosomal acidification defects and reduced expression of cathepsin L, hindering the degradation of lysosomal substrates (Inami et al., 2011); (5) defects in autophagosome-lysosome fusion (Koga et al., 2010); and (6) accumulation of excessive triglycerides and free fatty acids due to insulin resistance and oxidative stress, triggering lipotoxicity and further inhibiting autophagic activity (Fukuo et al., 2014; Ueno and Komatsu, 2017). Notably, insulin can inhibit autophagy by activating mTORC1, resulting in the phosphorylation of UNC-51-like kinase 1 (ULK1) and the inactivation of forkhead box O (FoxO) transcription factors (Frendo-Cumbo et al., 2021). Liver autophagy is similarly impaired in individuals with obesity, NAFLD, and insulin resistance (Ezquerro et al., 2019). Excessive cellular nutrients in NAFLD could activate mTOR, which, once overactivated, would increase adipogenesis, inhibit autophagy, and disrupt lysosomal biogenesis. Increased lipogenesis, insufficient autophagy, and reduced lysosomes contribute to hepatic steatosis and then lead to lipotoxicity. Therefore, activating lysosomes and/or ALP in liver cells may be a therapeutic approach for NAFLD.

3.3 Inflammation-associated diseases

Recently, studies have demonstrated that autophagic regulatory mechanisms are crucial for maintaining cellular homeostasis and survival when cells are in a state of inflammation, hypoxia, and nutrient deprivation. These mechanisms enable cells to adapt to the stresses in the internal and external microenvironments while preserving their normal physiological functions (Ceccariglia et al., 2020; He JL et al., 2021).

3.3.1 Pancreatitis

Extensive reports have confirmed the correlation between acute pancreatitis and ALP. The decreased maturation of cathepsin B and cathepsin L, increased formation of autophagosomes, and decreased lysosomal degradation ability reflect lysosomal dysfunction caused by pancreatitis (Mareninova et al., 2009, 2015; Gukovskaya and Gukovsky, 2012). Additionally, impaired lysosomal hydrolytic activity is evidenced by the accumulation of large autolysosomes containing partially digested cargo. Two mechanisms are reportedly responsible for the autophagic impairment in pancreatitis, involving a lack of lysosomal proteolytic activity and pathological changes to lysosomal membrane proteins (Gukovskaya and Gukovsky, 2012). In addition to abnormal proteases, the disruption of ATG5 (Diakopoulos et al., 2015), ATG7 (Antonucci et al., 2015), or LAMP2 (Mareninova et al., 2015) could also induce spontaneous or chronic pancreatitis, indicating

that lysosome and/or ALP play crucial roles in the pathology of pancreatitis.

3.3.2 Periodontitis

Periodontitis is one of the most common chronic inflammatory diseases, leading to tissue damage that gradually penetrates periodontal tissues, ultimately resulting in tooth loss and causing serious damage to oral function and health (Seo et al., 2004; Hu et al., 2018; Li Q et al., 2020). Various therapeutic interventions have been used to treat periodontitis clinically, but the results have been less than satisfactory. In regenerative dentistry, periodontal ligament stem cells (PDLSCs) are easily isolated and can differentiate into precursor cells to form multiple periodontal tissues (Queiroz et al., 2021). PDLSCs are the most suitable for regenerating periodontal tissues. Recently, research has indicated that the autophagic process is crucial for maintaining cellular homeostasis and differentiation. Dysfunction of autophagy can lead to metabolic disorders, which ultimately compromise the stemness and regeneration of stem cells. Yin et al. (2022) constructed an inflammatory cell model (PDLSCs cultured under inflammatory conditions (I-PDLSCs)) and found that levels of autophagy and autophagic flux decreased in I-PDLSCs. The ALP is crucial to the cellular osteogenic differentiation process, and it can be used as a novel target to reverse inflammatory damage to the possibility of osteogenic differentiation of cells, offering new insights into the regulation of stem cell fate under specific conditions.

3.3.3 Atherosclerosis

The occurrence, development, and rupture of plaques in atherosclerosis are associated with damage to vascular cells, including macrophages, endothelial cells, and smooth muscle cells (Lin et al., 2022). Owing to plaque growth and thrombosis, atherosclerosis may progress to conditions such as coronary artery syndrome (Ahmadi et al., 2019), ischemic stroke (Herrington et al., 2016), intermittent claudication (Hamburg and Creager, 2017), and arterial aneurysm (Peshkova et al., 2016). During the development of the lesion, monocytes are recruited to the subendothelial layer of the blood vessels and differentiate into macrophages to remove cellular debris and retained lipids (Moore et al., 2013). However, the gradual uptake of poorly digestible modified lipids can result in the accumulation of partially digested or undigested cholesterol esters and free cholesterol in lysosomes (Jerome et al., 2008). The expression profile of ATGs confirms the close association between autophagy and atherosclerosis (Chen et al., 2021). There are various autophagy inducers in atherosclerotic plaque, such as low-density lipoprotein, tumor necrosis factor-α (TNF-α), inflammatory mediators, and ROS (Shao et al., 2016; Zhu et al., 2019). Mild cellular stress, including oxidized low-density lipoprotein, oxidative stress, and endoplasmic reticulum stress, can induce mild adaptive autophagy of vascular cells (Menghini et al., 2014) and degrade damaged organelles and proteins to promote cell survival. Autophagy can increase anti-inflammatory macrophages, vascular smooth muscle cells, and collagen content, and then reduce lipid deposition and cell death within the plaques to effectively maintain a stable plaque phenotype (Moore et al., 2013). Autophagy markers ATG13 and LC3 are significantly up-regulated in the aortic intima endothelial cells of patients with severe atherosclerosis compared to patients without atherosclerosis (Labrijn et al., 2017). Similarly, autophagic dysfunction occurs during the development of atherosclerosis, regardless of whether there is autophagic stimulation in atherosclerotic plaques, which will exacerbate atherosclerosis. Excessive autophagy caused by severe oxidative stress or inflammatory stimulation results in autophagy-dependent cell death, reduced collagen synthesis, thinning of the fibrous cap, unstable plaques, lesional thrombosis, restenosis, and acute coronary events (Cai et al., 2018; Ge et al., 2021). Therefore, in the early stages, resisting excessive autophagy is crucial for preventing atherosclerosis and severe cardiovascular complications. Additionally, in the late stage of lesions with abundant oxidative stress, autophagy may be insufficient to deal with excessive stress within the plaques, leading to cell apoptosis.

3.4 Aging

Aging is a biological process in which the functions of cells and organisms decrease over time, leading to a decline in an individual's quality of life (Leidal et al., 2018). Concurrently, aging is accompanied by the occurrence of cardiovascular diseases (e.g., stroke), cancers, and neurodegenerative diseases. Aging-related diseases have become a significant global socioeconomic burden and health challenge

(Partridge et al., 2018; Fang et al., 2020). Studies at the cellular and molecular levels reveal that the compromised autophagy, impaired autophagy-lysosome signaling pathway, and mitochondrial dysfunction have become characteristic features of aging in different species (Mattson and Arumugam, 2018; Schmauck-Medina et al., 2022; López-Otín et al., 2023). The autophagic activity and lysosomal function of different organisms decrease with aging, thereby exacerbating cellular damage and promoting the development of age-related diseases (Leidal et al., 2018; Lou et al., 2020; Sun et al., 2020). Additionally, the expression of autophagy-related genes (such as *ATG*s, *LC3*, *TFEB*, and *SQSTM1*/*p62*) is crucial for the initiation and activity of autophagy, which is associated with aging-related diseases (Miceli et al., 2023). Rescuing autophagic function would be a promising therapeutic mode for age-related diseases. TFEB activation could restore the lysosomal biogenesis and autophagic flux, thus delaying aging or increasing lifespan in aging-related diseases (Abokyi et al., 2023). It is indicated that glycine supplementation plays a paramount role in improving health and prolonging life by activating autophagy for aging-related diseases (Johnson and Cuellar, 2023). Nicotinamide adenine dinucleotide (NAD/NAD^+) could regulate autophagy, and conversely, autophagy could regulate the expression level of NAD, thereby maintaining cellular activity. NAD could be hydrolyzed by NAD^+-consuming enzymes (NADases) to downregulate the autophagic activity (Wilson et al., 2023). Significantly, some of the literature shows that mitochondrial dysfunction and NAD depletion affect neurodegeneration and aging, and supplementation of NAD restores the function of mitophagy and increases the repair of DNA and the lifespan in various model systems (Fang et al., 2014, 2016; Presterud et al., 2024).

4 Nanoparticles rescuing lysosomal/autophagic defects for disease interventions

After being engulfed by cells, nanoparticles generally enter lysosome-associated acidic organelles. Therefore, it is expected that rationally designed nanoparticles can serve as ideal tools for regulating lysosomal function. In this section, we review the reported nanoapproach that can regulate lysosomal acidification and its applications in disease treatment.

4.1 Acidic nanoparticles

Acidic nanoparticles, including poly(lactic-co-glycolic) acid (PLGA)- or polylactic acid (PLA)-based acidic nanoparticles, succinate-based polymeric nanoparticles, and acidic nucleolipids, were reported to restore the acidity and degradation ability of lysosomes. In this section, we review the acidic nanoparticles with the reported ability to restore lysosomal acidity and autophagic flux and their roles in disease intervention (Table 1). Several aspects should be considered when synthesizing novel materials or reagents for regulating lysosomal pH: (1) Nanomaterials should be capable of internalizing into cells and locating within lysosomes; (2) nanomaterials should contain stimuli-responsive and/or biodegradable covalent linkages to ensure effective degradation of materials within lysosomes; and (3) a functional group released from the degradation process is acidic to restore the lysosomal pH (Fig. 3).

4.1.1 PLGA- or PLA-based acidic nanoparticles

Polymer nanoparticles such as PLGA and PLA have been widely used for their multiple advantages, including biodegradability, biocompatibility, simplicity of interaction, and targeted modification, as well as sustained/flexible drug release (Anderson and Shive, 1997; Kumari et al., 2010; Mahapatro and Singh, 2011). Considering that PLGA and PLA can be hydrolyzed to produce lactic acid and/or glycolic acid (GA), the question of whether these polymeric nanoparticles can restore lysosomal acidity and functionality in pathological conditions by targeting lysosomes has emerged. To our knowledge, the first report on the restoration of damaged lysosomal acidity and functionality by PLGA and PLA was published in the *PLoS ONE* journal (Baltazar et al., 2012). In this report, Baltazar et al. (2012) revealed that acidic polymeric nanoparticles composed of PLGA 502 H (PLGA Resomer® RG 502 H), PLGA 503 H (PLGA Resomer® RG 503 H), or PLA 203 S (PLA Resomer® R 203 S) could be localized in the lysosomes of human retinal pigment epithelial cells within 60 min, and nanoparticles composed of PLGA 503 H or PLA exhibited a stronger ability to restore the lysosomal pH after internalization into the lysosomal compartment. Additionally, the authors also verified that the reacidification of lysosomes induced by acidic nanoparticles composed of PLA was adequate to enhance the activity of

Table 1 Acidic nanoparticles capable of restoring lysosomal or autophagic function

Biomaterial type	Characteristics	Composition	Disease	Model	Biological effect	Reference
PLGA or PLA acidic nanoparticles	PLGA 502 H: 503.9 nm; PLGA 503 H: 387.4 nm; PLA: 428.5 nm	PLGA Resomer® RG 502 H; PLGA Resomer® RG 503 H; PLA 203 S	Macular degeneration	ARPE-19 cells	Restoring lysosomal function	Baltazar et al., 2012
PLGA acidic nanoparticles	50–100 nm	Resomer® RG 503H PLGA	PD	BE(2)-M17 cells; mutant ATP13A2, GBA, and X-linked myopathy with excessive autophagy fibroblasts	Restoring lysosomal function	Bourdenx et al., 2016
PLGA nanoemulsions	(187.0±3.0) nm; (−35.7±0.4) mV	Nanoemulsions loaded with PLGA nanoparticles	PD	BE(2)-M17 cells	Rescuing impaired lysosomal pH	Prévot et al., 2018
PLGA nanoparticles	(149.8±0.9) nm; (−41.5±0.8) mV	PLGA Resomer® RG 503 H	PD	BE(2)-M17 cells	Restoring lysosomal function	Arotcarena et al., 2022
PLGA nanoparticles	GA:LA (0:100), (108.2±5.7) nm, (−30.8±1.1) mV; GA:LA (75:25), (98.7±6.2) nm, (−31.4±1.2) mV; GA:LA (50:50), (101.5±4.5) nm, (−30.2±2.1) mV	PLGA with different glycolic acid to lactic acid ratios (0:100; 75:25; 50:50)	PD	PC-12 cells	Reacidifying defective lysosomes, rescuing mitochondrial toxicity	Zeng et al., 2019a
PLGA nanoparticles		PLGA (50:50 resomer)	AD	Timed pregnant BALB/c mice	Protecting neurons against Aβ toxicity, restoring lysosomal membrane integrity	Wang et al., 2020
PLGA-grafted silica nanoparticles	(21.3±2.0) nm; +8 mV	Silica nanoparticles; PLGA Resomer™ RG 502 H	Dox-induced cardiotoxicity	Rat H9c2 cardiomyoblasts, neonatal rat ventricular myocytes	Improving lysosomal function, preventing Dox-induced cardiotoxicity	Santin et al., 2023
PLGA and PLA nanoparticles	60–150 nm	Polyethylene glycol hexadecyl ether, PLGA, PLA, polystyrene-*b*-polyacrylic acid	Atherosclerosis	C57BL/6J strain or *apoe*$^{-/-}$ mice on C57BL/6J background	Rescuing macrophage lysosomal dysfunction	Zhang XY et al., 2023
PLGA nanoparticles	About 100 nm, −27 mV	PLGA Resomer® RG 503H, lactic acid/glycolic acid 50:50	Type 2 diabetes	INS-1 cells	Lowering lysosomal pH, restoring autophagic flux	Zeng et al., 2019b
Photoactivatable, acidic nanoparticles (paNPs)	About 100 nm	2-Nitrobenzaldehyde, succinic acid *O*,*O*′-(2-((methacryloyloxy) methyl)-2-methylpro-pane-1,3-diyl) bis(1-(2-nitrophenyl)ethyl) disuccinate, 1,4-*O*-methacryloylhydroquinone	Diabetes	INS-1 832/13 cells; C57Bl6 male mice islet cells	Enhancing lysosomal acidity and function, restoring autophagy, improving insulin secretion	Trudeau et al., 2016
paNPs	About 100 nm	2-Nitrobenzaldehyde, succinic acid	Genetic disorders, neurodegenerative diseases, obesity, type 2 diabetes	INS-1 cells; C57BL/6J male mice islets	Restoring of lysosomal acidity, recovering mitochondrial turnover and function	Assali et al., 2019
Acid-activated acidic nanoparticles	About 100 nm; −30 to −25 mV	Tetrafluoro succinic acid, succinic acid, ethylene glycol, titanium isoproxide	NAFLD	C57BL/6J DIO, FVB/NJ, and C57BL/6N male mice; HepG2 cells	Restoring lysosomal acidity and autophagy, rescuing metabolic dysfunction	Zeng et al., 2023
Succinic acid-based acidic nucleolipids	150–200 nm; −35 to −25 mV	Nucleolipid, succinic acid	PD	BE(2)-M17 cells	Restoring functional lysosomal pH	Brouillard et al., 2021
Succinic acid-based acidic nucleolipids	150–200 nm; −40 to −30 mV	Succinic acid, nucleoside, lipid	PD	BE(2)-M17 cells	Recovering lysosomal pH	Brouillard et al., 2023

PLGA: poly(lactic-co-glycolic) acid; PLA: polylactic acid; ATP13A2: adenosinetriphosphatase (ATPase) cation transporting 13A2; GBA: glucocerebrosidase; ARPE-19: adult retinal pigment epithelial cell line-19; BE(2)-M17: human neuroblastoma BE(2)-M17 cell line; PC-12: pheochromocytoma 12; INS1: insulin-secreting cell line; NAFLD: non-alcoholic fatty liver disease; DIO: diet-induced obesity; HepG2: human hepatocellular carcinoma cell line G2; PD: Parkinson's disease; AD: Alzheimer's disease; Aβ: β-amyloid; Dox: doxorubicin.

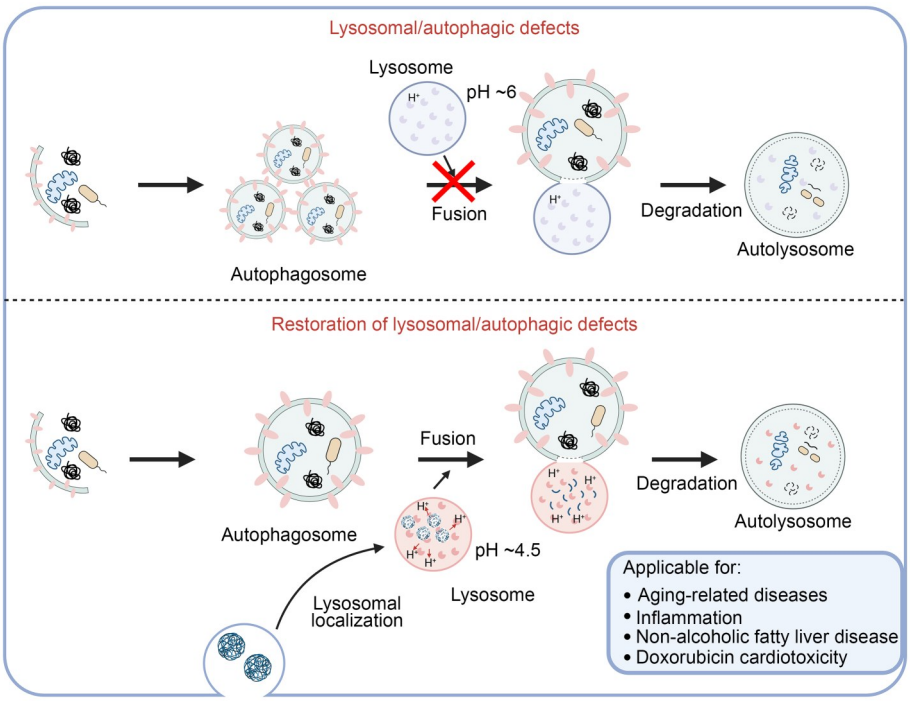

Fig. 3 Internalized lysosome-localized acidic nanoparticles restoring autophagy flux through lysosomal acidification mediated by the release of acidic functional groups. Created by BioRender.com.

lysosomal enzyme cathepsin D and can improve the clearance of photoreceptor outer segments in human retinal pigment epithelial cells.

Enhancing or restoring lysosome-mediated degradation is considered a promising intervention strategy for PD. Bourdenx et al. (2016) validated that acidic nanoparticles formed by PLGA could restore the damaged lysosomal acidity and functionality in various pathological cells or disease models. Their reports demonstrated that acidic nanoparticles prepared from PLGA (PLGA Resomer® RG 503 H with a lactide: glycoside ratio of 50:50, molecular weight 24 000 to 38 000) could be transported to lysosomes within 24 h and restore the acidity of chloroquine (CQ)-alkalized lysosomes, inhibiting CQ-elicited cytotoxicity. 1-Methyl-4-phenylpyridinium ion (MPP^+), the active form of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), is one kind of neurotoxin that induces PD-related changes in cells. Acidic nanoparticles could rescue MPP^+-induced lysosomal acidification defects and protect cells from mitochondrial-derived free radicals. Additionally, acidic nanoparticles could restore the acidity and functionality of damaged lysosomes in genetically modified cell models related to PD, namely ATP13A2-mutated or deficient cells, glucocerebrosidase (GBA)-mutated cells, and genetic models of lysosomal-related myopathies. Considering the limited diffusion of PLGA acidic nanoparticles in the brain due to the administration of PLGA via stereotactic injection, Prévot et al. (2018) further developed an oil-in-water (O/W) nanoemulsion (NE) loaded with PLGA (denoted as NE-PLGA). NE-PLGA, exhibiting a high-PLGA payload, could enter the lysosomal compartments and restore the pH of damaged lysosomes in a PD-related genetic cell model. After stereotactic injection of the nanoparticles into the substantia nigra of mice, NE-PLGA was widely diffused from the injection site by up to 500 μm. It was also evidenced that these nanoparticles could cross the blood–brain barrier, be internalized by cells, and reside in lysosomes, demonstrating a targeted lysosomal delivery and restoration of the lysosomal acidity therapeutic mode. Additionally, Zeng et al. (2019b) found that acidic nanoparticles formed by PLGA with a high GA to lactate (LA) ratio (GA:LA) were degraded faster in MPP^+-treated pheochromocytoma 12 (PC-12) cells, and exhibited stronger capabilities in terms of restoring lysosomal acidity and autophagic flux. Recently, Arotcarena et al. (2022) validated acidic PLGA nanoparticles' ability to enhance α-syn degradation

by increasing lysosomal activity. These findings support lysosomal reacidification as a viable therapeutic approach for PD and other age-related diseases.

PLGA-based acidic nanoparticles have the potential to protect neuronal cells from Aβ toxicity by restoring lysosomal membrane integrity, thus providing the distinctive therapeutic possibilities in addressing AD. Wang et al. (2020) found that the toxicity induced by $A\beta_{1\text{-}42}$ in cortical-cultured neurons is related to the compromised lysosomal integrity, increased phosphorylation of tau, and levels of carbonylated proteins. However, PLGA nanoparticle treatment could alleviate Aβ toxicity by depressing the levels/distribution/activity of cathepsin D, carbonylated proteins, and tau phosphorylation. The study demonstrates that the cytosol level, along with the activity of cathepsin D, confers neuronal vulnerability in AD and showcases the capability of PLGA-formulated nanoparticles for restoring lysosomal integrity and shielding neurons from Aβ toxicity, indicating its promising utility in addressing AD.

In addition, PLGA-based acidic nanoparticles can alleviate doxorubicin (Dox)-induced cardiotoxicity by improving lysosomal function. While most previous studies have suggested that mitochondrial and DNA damages are the mechanisms behind Dox-induced cardiotoxicity, recent findings suggest that the blockage of autophagy resulting from the lysosomal acidification defect may contribute to the pathogenesis of Dox-induced cardiomyopathy (Li et al., 2016, 2018; Koleini and Kardami, 2017). Santin et al. (2023) designed PLGA-grafted silica nanoparticles (NPs-PLGA) and demonstrated their protective effects and mechanisms against Dox-induced cardiomyocyte toxicity. They found that NPs-PLGA could be rapidly internalized in cardiomyocytes and accumulate within lysosomes. Additionally, NPs-PLGA could alleviate Dox-induced lysosomal alkalinization, restore lysosomal function and autophagic flux, relieve Dox-induced early and persistent damage to the mitochondrial oxidative phosphorylation system, and attenuate Dox-induced oxidative stress and apoptosis. The results illustrate the crucial involvement of lysosomal dysfunction in Dox-induced cardiomyopathy and, for the first time, emphasize that the use of inhaled NPs-PLGA represents a promising approach to combating the cardiotoxicity associated with anthracycline drugs (Fig. 4).

PLGA-based core-shell acidic nanoparticles could be used as an intervention for atherosclerosis by restoring the lysosomal functional defects in macrophages. Typically, nanoparticles are indiscriminately taken up by mononuclear phagocytic cells, such as

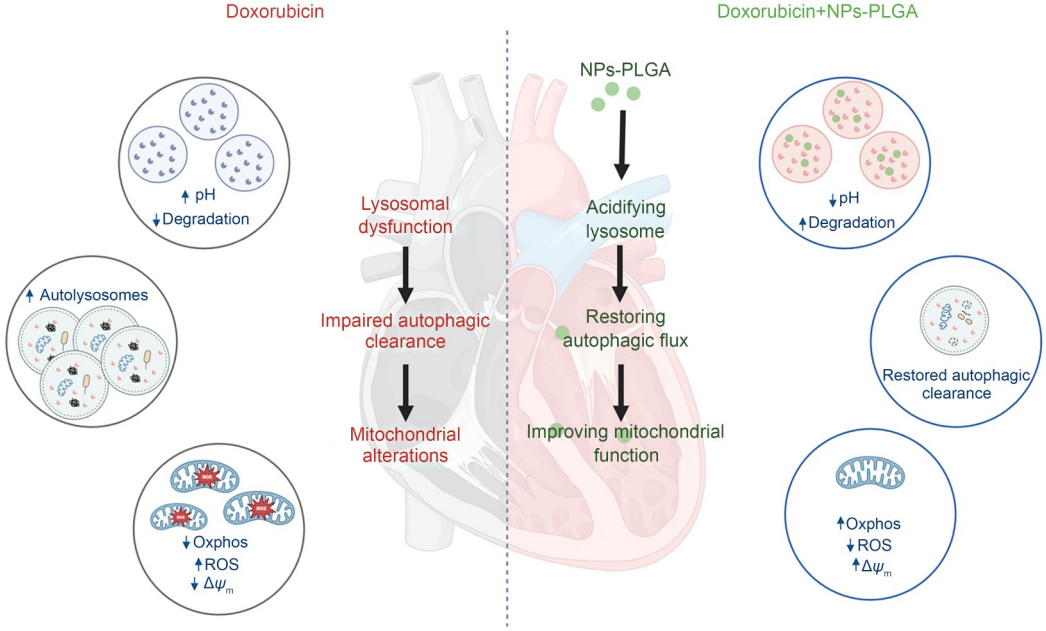

Fig. 4 Diagram of the inhalation of poly(lactic-co-glycolic) acid (PLGA)-grafted silica nanoparticles (NPs-PLGA) offering the protection against doxorubicin (Dox)-induced cardiotoxicity by restoring lysosomal function. Created by BioRender.com according to Santin et al. (2023). Oxphos: oxidative phosphorylation; ROS: reactive oxygen species; $\Delta\Psi_m$: mitochondrial membrane potential.

monocytes and macrophages, potentially resulting in the degradation of cargo in lysosomes. Zhang XY et al. (2023) constructed core-shell acidic nanoparticles based on PLA and PLGA, and exploited them to target macrophage lysosomes, restoring their pH levels in conditions such as atherosclerosis. Both types of acidic nanoparticles were effectively internalized by cells and localized within lysosomes; however, only PLGA-based core-shell acidic nanoparticles were more efficient in promoting lysosomal acidification. Additionally, they showed the practicality of PLGA-based core-shell acidic nanoparticles in vivo and revealed the accumulation of nanoparticles in macrophages within atherosclerotic plaques and enhanced lysosomal acidification. Prolonged use of PLGA nanoparticles significantly reduced plaque complexity indicators and macrophage apoptosis. This research demonstrated the promising application of acidic nanoparticles in restoring lysosomal dysfunction in macrophages, offering a potential therapeutic approach for treating atherosclerosis (Fig. 5).

In pancreatic β cells, prolonged exposure to a high level of fatty acids can lead to lipotoxicity (Las et al., 2011; Mir et al., 2015) and autophagic dysfunction, along with impaired lysosomal acidity. Zeng et al. (2019b) validated that acidic nanoparticles formed by PLGA assembly improved lysosomal pH and size, and restored autophagic flux and insulin secretion in pancreatic β cells under high fatty acid exposure. Upon the addition of NPs-PLGA, the extent of lysosomal pH restoration rises in proportion to the concentration of NPs-PLGA, which is attributed to an increase in acidic group release, leading to a reduction in lysosomal pH, as well as a decrease in the average size of lysosomes. Meanwhile, NPs-PLGA could reduce the accumulation of lipidated LC3 (LC3-II) and SQSTM1/p62 induced by palmitate salts, indicating an overall improvement in autophagic flux due to increased

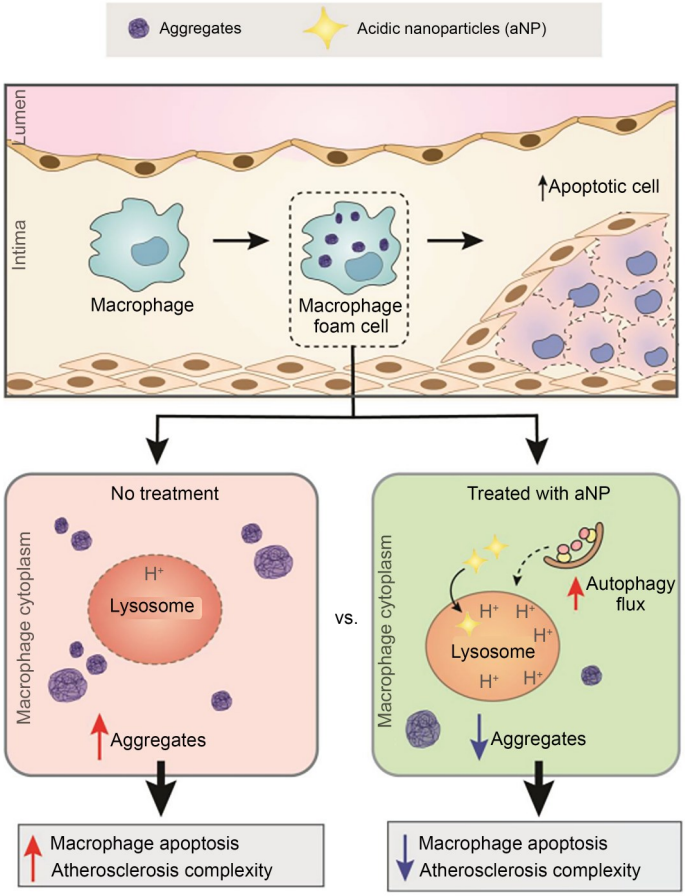

Fig. 5 Pattern diagram for rescuing macrophage lysosomal dysfunction using poly(lactic-co-glycolic) acid (PLGA) nanoparticles in atherosclerosis. Created by BioRender.com. Reprinted from Zhang XY et al. (2023) by permission of Taylor & Francis Ltd.

autophagic degradation and clearance of accumulated autophagosomes. Treatment with NPs-PLGA also significantly restored the impaired glucose-stimulated insulin secretion with exposure to palmitate salts. In summary, the use of functional nanoparticles to restore lysosomal function and autophagic flux in pancreatic β cells presents a promising novel approach for addressing lysosomal dysfunction-related disorders.

4.1.2 Succinate-based polymeric nanoparticles

Prolonged exposure to a high level of fatty acids (lipotoxicity) can lead to the inhibition of autophagic flux in pancreatic β cells, liver cells, and myocardial cells, accompanied by a decrease in lysosomal acidity. To ascertain whether lysosomal acidification damage is the cause of the inhibition of autophagy and cellular functions, Trudeau et al. (2016) found that photoactivatable acidic nanoparticles (paNPs) based on succinic acid could localize within lysosomes, enhance lysosomal acidity and function, restore autophagic flux, and stimulate insulin secretion. Since both lysosomes and mitochondria can influence each other's functions, it is unclear which dysfunction triggers the harmful cascade reaction of lipotoxicity that ultimately leads to β-cell failure. Assali et al. (2019) studied the impact of reinstating lysosomal acidity on mitochondrial function in response to lipotoxicity. They showed that paNPs could release acidic components that can regulate lysosomal acidity under the stimulation of light, thereby promoting the recovery of lysosomal acidity under lipotoxicity and accelerating mitochondrial turnover. Notably, the nanoparticle-facilitated lysosomal re-acidification restored citrate synthase activity and adenosine triphosphate levels, and rescued the maximum respiratory capacity of mitochondria in INS-1 cells and primary mouse pancreatic islets.

Recently, Zeng et al. (2023) showed that acid-activatable acidic nanoparticles (AcNPs) could target lysosomes and promote lysosomal re-acidification and autophagy flux. AcNPs, composed of fluorinated polyesters, exhibit no activity at plasma pH, while being activated upon entering lysosomes after cellular endocytosis. They could be degraded at a pH of approximately 6, which is characteristic of impaired lysosomes, and release acidic groups to acidify and enhance lysosomal function. AcNP treatment could rescue the reduced autophagic flux, restore lysosomal protein hydrolysis function, reduce lysosomal pH and average lysosomal size, improve insulin sensitivity, and restore the mitochondrial activity of human hepatocellular carcinoma cell line G2 (HepG2) cells treated with palmitate salts. Intravenous injection of AcNPs significantly improved liver damage, reduced C-peptide levels and fasting insulin, restored impaired glucose tolerance and insulin sensitivity, and reversed hepatic steatosis in high-fat diet mice. Reacidifying lysosomes with AcNP treatment restored autophagy and mitochondrial function to normal levels. This restoration, along with the correction of fasting hyperglycemia and hepatic steatosis, suggests that AcNPs may be a preferred treatment for NAFLD (Fig. 6).

4.1.3 Acidic nucleolipids

Nucleolipids are small molecules designed through bioinspiration, consisting of lipids covalently linked to nucleic acid derivatives, nucleobases, nucleosides, nucleotides, or oligonucleotides, that have structural characteristics similar to those of cell membranes (Gissot et al., 2008). Nucleolipids can be either natural or synthetic. Regardless of their origin, in addition to their biological activities, such as antibacterial, antifungal, or antitumor properties, they all have self-assembly capabilities (van Tiel et al., 1985; Simeone et al., 2011; Riccardi et al., 2017). Nucleolipids are commonly considered as delivery carriers for active drugs, with documented capability to cross the blood–brain barrier (Swastika et al., 2019). NEs have certain advantages in delivering active drugs to the brain. O/W NEs are composed of submicron-sized oil droplets that are stabilized by shells composed of amphiphilic surfactants, exhibiting better stability and higher loading capacity for hydrophobic drugs or imaging probes.

Appropriately functionalized nucleolipids could be encapsulated into O/W NEs, effectively internalized into human neuronal cells, and finally localized within lysosomes (Cunha et al., 2020). Brouillard et al. (2021) carried out the synthesis, formulation, and biological assessment of nucleolipids carrying organic acid moieties, and demonstrated that they can be used as prodrugs and potential pro-lysosomal acidification agents (Fig. 7a). Succinic acid was selected because of its good biocompatibility and its pK_a (negative base 10 logarithm of the acid dissociation constant K_a) closely resembling that of lactic acid and GA; the free acids help nucleolipids acidify quickly. Conversely, the second acid functional group protected in ester

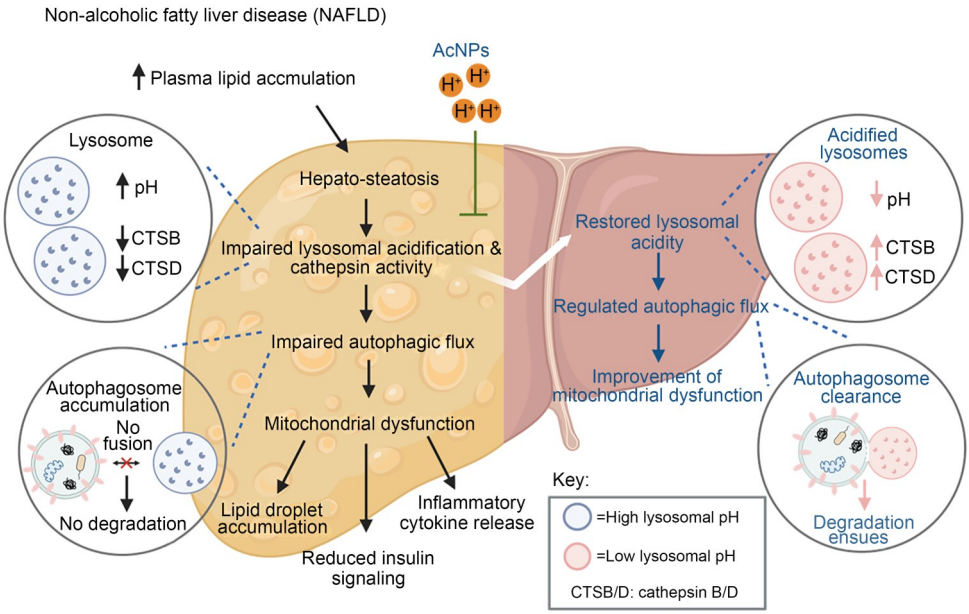

Fig. 6 Impact of impaired lysosomal function in non-alcoholic fatty liver disease (NAFLD) and the mechanism of action of acid-activatable acidic nanoparticles (AcNPs). Created by BioRender.com according to Zeng et al. (2023).

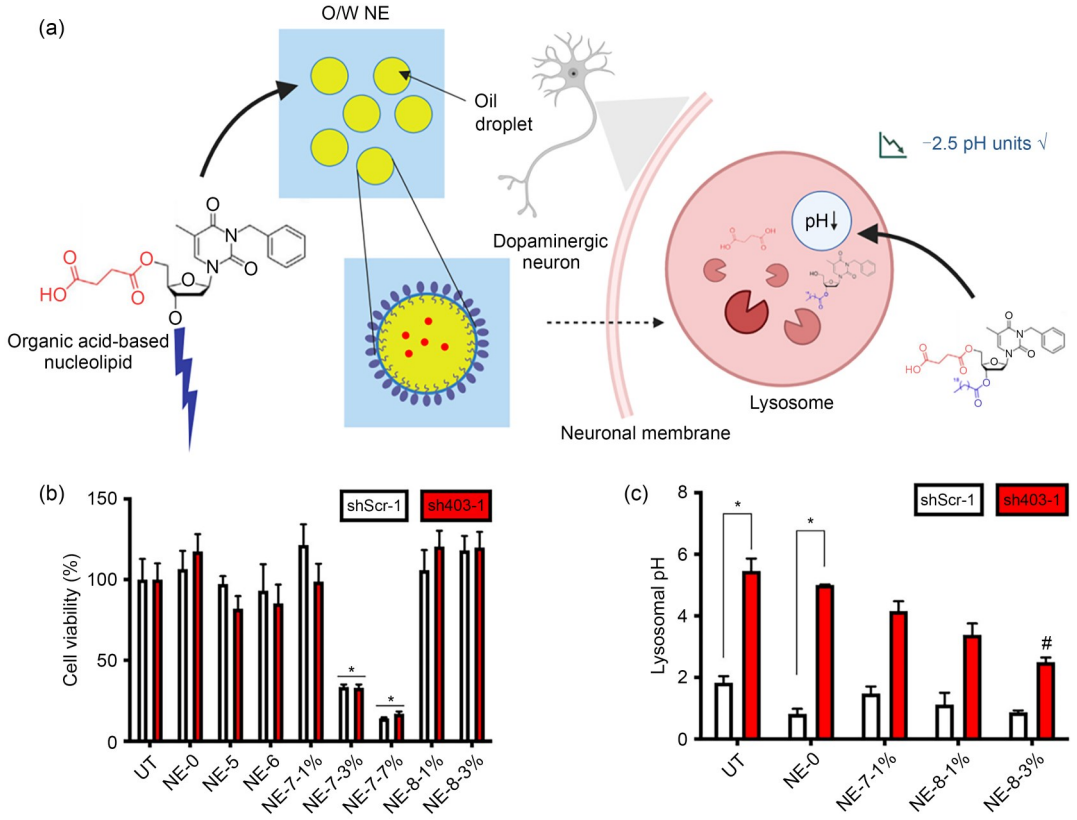

Fig. 7 Nucleolipidic nanoemulsions (NEs) for neuronal lysosomal acidification. (a) Illustration of acidification of neuronal lysosome using nucleolipidic NEs, which was redrawn with BioRender.com according to Brouillard et al. (2021). O/W NE: oil-in-water nanoemulsion. (b) Cell viability in control and adenosinetriphosphatase (ATPase) cation transporting 13A2 (ATP13A2)-depleted M17 cells. (c) Acidic NEs restore lysosomal pH in vitro. Reproduced from Brouillard et al. (2021) licensed under Creative Commons CC BY 4.0.

form at the 5' position will be liberated for a subsequent acidification upon enzymatic cleavage. The designed nucleolipids were formulated into O/W NEs to allow them to cross the plasma membrane. The properties of the 3' position fatty chain were modulated to investigate the influence of lipid chain length on cytotoxicity and acidification ability (Figs. 7b and 7c). The encouraging results suggested that O/W NEs loaded with acidic nucleolipids could function as efficient nanocarriers for active drugs. Since damage to an adenosinetriphosphatase (ATPase) cation transporting 13A2 (ATP13A2) function can increase lysosomal pH, lysosomes in M17 neuroblastoma cells, where ATP13A2 was stably deleted, displayed an abnormally high pH. It has been demonstrated that acidic nucleolipids are readily transported to lysosomes and effectively restore the pH of impaired lysosomes.

Brouillard et al. (2023) synthesized a DNA-derived nanocarrier, in which the nucleolipids are covalently linked to lipids with biocompatible organic acids as active components. They could be effectively integrated into O/W NE carriers and be capable of traversing biological membranes and releasing effective biocompatible acidic components to restore lysosomal acidity in neuronal cells. A biological analysis of a PD genetic cell model emphasized the non-toxicity of these nucleolipid post-cellular uptake and their ability to completely restore lysosomal acidity at 40 μmol/L. From a pharmaceutical perspective, to enhance the stability and reduce overall concentration of nucleolipid-based prodrugs, nucleolipid oligomerization emerged as an interesting chemical modification (Brouillard et al., 2021). Subsequently, Brouillard et al. (2021) designed oligomerized compounds, which were successfully dissolved into the oil phase of the O/W NEs, allowing them to traverse biological membranes. These experiments validate the therapeutic promise of novel nucleolipid-based nanosystems and underscore lysosomal restoration as a promising strategy for the treatment of PD and other age-related protein diseases.

4.2 Inorganic non-metallic nanoparticles

Several kinds of inorganic non-metallic nanoparticles, including graphene oxide (GO), nano-selenium, carbon nanotubes, and graphene quantum dots (GQDs), have been reported to enhance lysosomal acidity and function and enhance autophagic flux, demonstrating their potential in the intervention of neurodegenerative diseases (Table 2).

4.2.1 Graphene oxide

Liu et al. (2016) explored the impact of GO on polychlorinated biphenyl (PCB)-induced cytotoxicity. They demonstrated that pre-treatment with GO could reduce the cytotoxicity induced by 2,2,5-tetrachlorobiphenyl (PCB 52, an *ortho*-substituted noncoplanar congener) and mutations in the cluster of differentiation 59 (*CD59*) gene. Mechanistically, they found that GO could alleviate the cytotoxicity of PCB 52 by inducing autophagic flux in cells. Our research group reported that GO could induce autophagy flux and promote the clearance of mutant huntingtin protein in HD-associated cell models. The ubiquitination of the mutant huntingtin protein induced by GO treatment was found to be necessary for the GO-induced degradation effect (Jin et al., 2016). Although the regulation of lysosomal acidity by GO was not fully evaluated, our study suggested that GO could be localized to the structures of autophagosomes and autolysosomes, providing important insights for the design of nanomedicines targeting autophagosomes or autolysosomes (Jin et al., 2016). The abnormal accumulation of prion proteins with protease-resistant misfolded conformations is the pathological mechanism of prion diseases. Jeong et al. (2017) indicated that GO treatment could restore autophagic flux impaired by prion protein peptides, thereby inhibiting the cytotoxicity induced by prion protein peptides. GO has also been reported to inhibit the cytotoxicity caused by Aβ protein overloading via different molecular and cellular mechanisms (Mahmoudi et al., 2012; Yang et al., 2015; Chen X et al., 2023). Studies have also shown that enhancing autophagic flux can significantly promote the degradation of Aβ protein and effectively alleviate cytotoxicity. Li XL et al. (2020) clarified that GO could activate autophagic flux, stimulate the clearance of Aβ protein, and protect cells from Aβ protein-elicited toxicity in microglial BV2 cells and human neuroblastoma SK-N-SH cells by activating the adenosine monophosphate (AMP)-activated protein kinase (AMPK)-mTOR signaling pathway. Chu et al. (2021) further validated the neuroprotective effect of GO using a mouse model of AD. Zhang et al. (2020) further elaborated that GO could inhibit β-cleavage of amyloid precursor proteins and promote the delivery of intracellular Aβ

Table 2 Inorganic non-metallic nanoparticles capable of restoring lysosomal or autophagic function

Biomaterial type	Characteristics	Disease	Model	Mechanism of action	Concentration	Biological effect	Reference
GO	Single layer; large GO: 2.4 μm (hydrodynamic size), (−11.90±1.75) mV; small GO: 200 nm (hydrodynamic size), (−30.00±2.06) mV	HD	HeLa, PC-12 cells	Enhancing autophagic flux and ubiquitination of huntingtin protein	60 μg/mL	Enhancing the clearance of mutant huntingtin	Jin et al., 2016
	Mostly less than 1 μm; average thickness approximately 1 nm	Prion diseases	Human neuroblastoma cell line (SK-N-SH)	Restoring autophagic flux impaired by prion protein peptides	8 mg/L	Preventing prion-mediated mitochondrial neurotoxicity	Jeong et al., 2017
	Single-layer nanosheet shape; mostly less than 60 nm	AD	BV2 cells, SH-SY5Y cells	Activating autophagy via activating the AMPK-mTOR signaling	100 μg/mL	Promoting the clearance of Aβ	Li XL et al., 2020
	Single-layer nanosheet shape; about 200 nm (hydrodynamic size); (−30.00±2.06) mV	Postoperative cognitive dysfunction	HEK293T cells, SH-SY5Y cells, female C57BL/6 mice	Reducing Aβ generation, enhancing lysosome-mediated Aβ degradation	60 μg/mL	Improving cognitive function of the postoperative mice	Zhang et al., 2020
	0.945 nm (average thickness); (253.10±10.78) nm (hydrodynamic size); (−46.00±1.08) mV (charge)	Polychlorinated biphenyl (PCB)-induced toxicity	Human-hamster hybrid AL cells	Triggering mTOR-independent autophagy	10 μg/mL	Attenuating the cytotoxicity and genotoxicity of PCB 52	Liu et al., 2016
Nano-selenium	About 40 nm	Cd-induced testicular toxicity	TM3 cells	Inhibiting ROS production, recovering autophagic flux	20 μmol/L	Attenuating Cd-induced TM3 cell toxicity	Hu et al., 2023
SWNT	1–2 nm (average diameter)	AD	Primary glial cells from CRND8 mice	Reversing abnormal activation of mTOR signaling and deficits in lysosomal proteolysis	0.05 μg/mL	Facilitating elimination of autophagic substrates	Xue et al., 2014
GQD	(2.25±0.57) nm (average lateral size), (1.86±0.22) nm (height)	Niemann-Pick disease type C	Induced neural stem cells derived from NPC1 patients, *NPC1*-knockout mice	Inhibiting the atypical accumulation of cholesterol, reducing the abnormal accumulation of autophagic vacuoles	In vitro: 1 μg/mL; in vivo: 50 μg/mL	Restoring autophagic flux, protecting against the loss of Purkinje cells in the cerebellum	Kang et al., 2021

GO: graphene oxide; SWNT: single-walled carbon nanotube; GQD: graphene quantum dot; Cd: cadmium; HD: Huntington's disease; AD: Alzheimer's disease; PCB 52: 2,2,5-tetrachlorobiphenyl; HeLa: Henrietta Lack; PC-12: pheochromocytoma 12; AMPK: adenosine monophosphate (AMP)-activated protein kinase; mTOR: mechanistic target of rapamycin; Aβ: β-amyloid; ROS: reactive oxygen species; TM3 cells: mouse testicular interstitial cells; NPC1: Niemann-Pick disease type C intracellular cholesterol transporter 1.

to lysosomes, thereby alleviating Aβ overloading. They also evaluated its positive role in postoperative cognitive dysfunction in a mouse model, which is associated with central nervous system diseases related to Aβ deposition.

4.2.2 Nano-selenium

Nano-selenium also exhibits unique biological effects, which have attracted increasing attention (He LN et al., 2021). Nano-selenium has been reported to restore impaired cellular autophagic flux. Cadmium is known to be an environmental pollutant that can induce oxidative stress and cause male reproductive toxicity. It was reported that nano-selenium could potentially improve testicular toxicity induced by cadmium. Hu et al. (2023) selected mouse testicular interstitial (TM3) cells and verified that cadmium could block autophagy flux and promote the production of ROS, thereby inducing testicular interstitial cell toxicity. Nano-selenium could significantly inhibit the production of cadmium-induced ROS, relieve cadmium-induced blockage of autophagy flux, and restore cell viability.

4.2.3 Carbon nanotubes

Carbon nanotubes have excellent physical properties, including a high electrochemically active surface area, effective thermal conductivity, superior electron conductivity, and exceptional mechanical strength, making them suitable for various applications in nanomedicine, such as stroke, neurological disorders, and schizophrenia (Kyle and Saha, 2014). Xue et al. (2014) investigated the potential of single-walled carbon nanotubes (SWNTs) to upregulate autophagy at non-toxic concentrations and reverse autophagic turnover defects in astrocytes in an AD mouse model. SWNT treatment could decrease the abnormally high phosphorylation level of mTOR in primary glial cells from CRND8 mice and restore autophagy induction. In addition to the impairment of autophagy initiation, primary glial cells from CRND8 mice also exhibited significant lysosomal dysfunction, as evidenced by the restricted maturation of cathepsin D, lysosome swelling, and the accompanying decrease in the number of lysosomes. SWNT treatment could restore the maturation and activity of cathepsin D in the primary glial cells derived from CRND8 mice. The significant enlargement and reduced quantity of lysosomes were also corrected by SWNTs. These functionalized SWNTs can reverse the aberrant activation of the mTOR signal and repair lysosomal proteolysis defects, thereby restoring autophagy and promoting the clearance of autophagic substrates.

4.2.4 Graphene quantum dots

GQDs have several unique properties, including small size, amphiphilicity, bio-compatibility, and easy modification by various functional groups, making them suitable for various applications in nanotechnology and nanomedicine (Ghazali et al., 2023). Kim et al. (2018) found that GQDs could inhibit the fibrillization of mutant α-syn, thereby protecting neurons in PD. Kang et al. (2021) evaluated the potential of GQDs to treat the Niemann-Pick disease type C intracellular cholesterol transporter 1 (*NPC1*)-knockout mice model and the induced neural stem cells derived from NPC1 patients. Treatment with GQDs could inhibit atypical accumulation of cholesterol, reduce abnormal accumulation of autophagic vacuoles, restore autophagic flux, and finally protect against the loss of Purkinje cells in the cerebellum.

4.3 Metal-based nanoparticles

Gold nanoparticles (AuNPs), cerium oxide nanoparticles (nanoceria), zinc oxide (ZnO) nanoparticles, and others have been reported to enhance lysosome and/or ALP activity (Table 3). Most studies suggest that TFEB, a key transcription factor managing the expression of ALP-related genes, is the main regulatory mechanism for metal-based nanomaterials to modulate lysosomal activity and ALP activity (Fig. 8).

4.3.1 Gold nanoparticles

AuNPs can modulate the cellular autophagic process through surface chemistry (Li et al., 2015; Ma et al., 2017) or size-dependent mechanisms (Chithrani et al., 2006; Chithrani and Chan, 2007; Ma et al., 2011). Although most reports indicate that AuNPs can inhibit cellular autophagy by damaging lysosomes (Ma et al., 2011; Zhou et al., 2018) or interfering with autophagosome-lysosomal fusion (Wan et al., 2018), the intracellular uptake and subsequent lysosomal retention of AuNPs (Huang et al., 2023) provide an important clue for targeting interventions for lysosome-related diseases. Maysinger et al. (2020) found that gold nanoclusters surface-modified with glutathione

Table 3 Metal-based nanoparticles capable of restoring lysosomal or autophagic function

Biomaterial type	Characteristics	Disease	Model	Concentration	Biological effect	Reference
Gold nanoclusters	Surface-modified with glutathione or polyethylene glycol (PEG); about 3 nm	Glioblastoma	Human glioblastoma U251N cells	≤1 μmol/L	Regulating lysosome biology, causing hemostatic perturbations	Maysinger et al., 2020
AuNPs	40 nm	Periodontitis	PDLSCs	0.01 nmol/L	Promoting the activation of TFEB and inducing the upregulation of ALP-related genes; rescuing osteogenic potential of I-PDLSCs	Yin et al., 2022
Nanoceria	CeO_2-GlcNAc: (20.2±0.9) nm; CeO_2-PEG200: (20.5±0.8) nm; CeO_2-PEG1K: (25.9±0.5) nm; CeO_2-PEG10K: (29.6±0.7) nm; CeO_2-PVP10K: (25.9±0.4) nm; CeO_2-PVP40K: (32.8±0.5) nm	Neuronalceroid lipofuscinosis	HeLa cells, LINCL fibroblasts	0.01 mg/mL	Promoting the activation of TFEB and inducing the upregulation of ALP-related genes	Song et al., 2014
	$Ce(NO_3)_3·6H_2O$; ethylene glycol; NH_4OH	Age-related macular degeneration	Age-related pigment epithelium (ARPE)-19 cells	1 nmol/L	Modulating autophagy	Tisi et al., 2020
Nanoceria; nanoceria attached by zirconium oxide (CZNPs)	Nanoceria: 3–4 nm; CZNPs: 2 nm	Acute kidney injury	Hypoxic HK-2 cells	In vitro: 10 μg/mL; in vivo: 10 mg/kg	Attenuating hypoxia-induced acute kidney injury	Hong et al., 2020
Fe_3O_4	Spherical; (200.00±6.79) nm; (20.3±1.6) mV	*Salmonella* infection	Chicken	50 mg/kg	Regulating ROS, phosphorylation of mTOR, and autophagy	Shen et al., 2020
Fe_3O_4@BSA	102 nm; −18.6 mV	Chronic renal tubular injury	TIF C57BL/6 mice; *Rab7*-overexpressing transgenic mice with TIF	20 mg/kg	Reversing cationic BSA-induced kidney damage via rescuing MMP2 activity and restoring autophagy flux	Liu et al., 2021
Zinc oxide (ZnO) nanoparticles	Bare nano-ZnO: (157.0±8.1) nm; nano/coated ZnO: (143.7±5.9) nm	Late infantile neuronal ceroid lipofuscinosis	LINCL cells; TFEB-overexpressing HeLa cells	20 μg/mL	Activating TFEB-regulated ALP and the clearance of lipofuscin	Popp and Segatori, 2019
Europium hydroxide nanorods	A length of 80–160 nm and a diameter of 25–40 nm	HD	EGFP-Htt(Q74)-overexpressing Neuro-2A or PC-12 cells; HeLa cells	50 μg/mL	Enhancing lysosome acidity, maturation of cathepsin D, and clearing huntingtin protein aggregation	Wei et al., 2014, 2015

AuNPs: gold nanoparticles; PDLSCs: periodontal ligament stem cells; I-PDLSCs: inflamed PDLSCs; GlcNAc: *N*-acetylglucosamine; PEG: polyethylene glycol; PVP: polyvinylpyrrolidone; ROS: reactive oxygen species; mTOR: mechanistic target of rapamycin; MMP2: matrix metalloproteinase 2; TFEB: transcription factor EB; LINCL: late-infantile neuronal ceroid lipofuscinosis; BSA: bovine serum albumin; TIF: tubulointerstitial fibrosis; ALP: autophagy-lysosome pathway; EGFP: enhanced green fluorescent protein; HD: Huntington's disease; Htt(Q74): huntingtin protein with 74 polyglutamine repeats; Neuro-2A: neuroblastoma-2A; PC-12: pheochromocytoma 12.

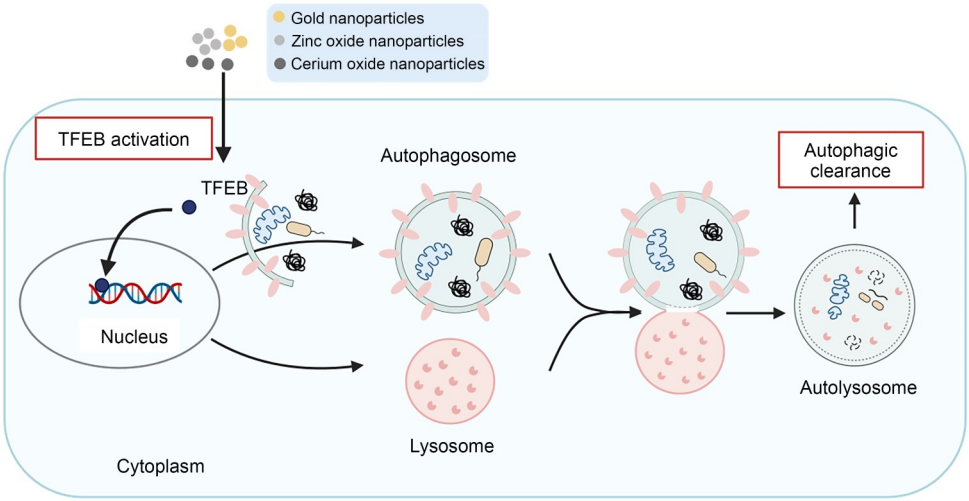

Fig. 8 Graphical illustration of the main regulatory mechanism of several metal-based nanomaterials in modulating lysosomal activity and autophagy-lysosome pathway activity. TFEB: transcription factor EB. Created by BioRender.com.

or polyethylene glycol (PEG), even at sub-lethal concentrations, could still modulate lysosomal abundance, localization, pH, and enzyme activity. Particularly, the biogenesis and stress response of lysosomes are promoted by stimulating the transient nuclear localization of TFEB and nuclear factor erythroid 2-related factor 2 (NRF2), suggesting the capability of AuNPs to regulate lysosomal biology. Recently, Yin et al. (2022) discovered that I-PDLSCs exhibited lysosomal swelling, a decrease in lysosome number, and autophagosome-lysosomal fusion disorder, which could be alleviated by the commercialized 40 nm AuNPs, indicated by the restoration of lysosomal size plus acidity and the enhancement of autophagosome-lysosome fusion and clearance of autophagic substrate proteins. Mechanistically, AuNPs could rescue the TFEB signaling pathway to enhance the lysosome- and autophagosome-associated gene expression and subsequently restore lysosomal degradation ability, exhibiting a certain recovery effect on the osteogenic possibility of I-PDLSCs (Fig. 9).

4.3.2 Cerium oxide nanoparticles

Nanoceria possess various biological effects, including antioxidant, anti-tumor, antibacterial, and neuroprotective properties (Kim et al., 2024), and have been utilized in the treatment of arthritis (Chen HY et al., 2023), tumors (Zhao et al., 2023), stroke (He et al., 2020), and chemotherapy-induced kidney damage (Weng et al., 2021). Nanoceria exhibit both free radical scavenging activity and catalytic activity. The cerium atom exists in the form of Ce^{3+} once zirconia is attached to ceria nanoparticles (CZNPs), enhancing the efficiency of their free radical scavenging. Hong et al. (2020) assessed the effectiveness of the antioxidant activity of ceria nanoparticles (CNPs) and CZNPs against acute kidney injury (AKI) caused by hypoxia. They found that CNPs and CZNPs could restore autophagic flux and mitigate mitochondrial damage, which in turn are conducive to the survival of hypoxic HK-2 cells. It was also illustrated that CZNPs could effectively alleviate hypoxia-induced AKI by protecting kidney structure and glomerular function.

Nanoceria have also been used to modulate the activity of the lysosome/ALP, which is expected to be used for interventions for age-related macular degeneration, neuronal ceroid lipofuscinosis, and other diseases. It was considered that nanoceria could promote the activation of TFEB and induce the upregulation of ALP-related genes responsible for the clearance of lipopigments. The dysfunction and degeneration of retinal pigment epithelium (RPE) contribute to age-related macular degeneration, playing a leading role in blindness worldwide. Tisi et al. (2020) found that nanoceria protected adult retinal pigment epithelial cell line-19 (ARPE-19) cells against H_2O_2-induced cell damage. Hong et al. (2020) applied an acute light-damaged rat model to mimic numerous characteristics of age-related macular degeneration. Intravitreal injection of nanoceria three days before light damage prevented RPE cell death and degeneration. They found that cerium dioxide nanoparticles were localized in the

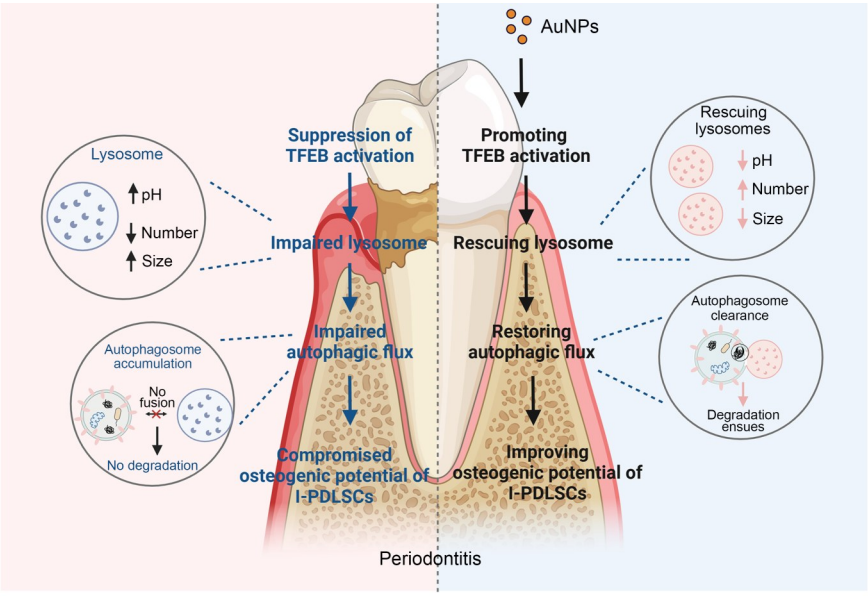

Fig. 9 Graphical illustration for restoring autophagy and osteogenic potential of inflamed periodontal ligament stem cells (I-PDLSCs) by gold nanoparticles (AuNPs). AuNPs could activate transcription factor EB (TFEB), restore lysosomal size and acidity, rescue autophagosome-lysosomal fusion, and improve autophagic activity and osteogenic potential in I-PDLSCs. Created with BioRender.com.

cytoplasm of RPE cells, and then suppressed the transition of epithelial-mesenchyme and regulated autophagy by downregulating LC3-II and SQSTM1/p62, thereby preventing RPE cell death and degeneration.

4.3.3 Iron-based metal oxides

Iron-based nanoparticles hold potential applications in various biomedical fields, such as magnetic navigation, drug delivery, and bioimaging. Specifically, iron oxide nanoparticles such as ferumoxytol have received the US Food and Drug Administration (FDA) approval for treating anemia. Iron-based nanoparticles could regulate cellular autophagy by virtue of surface chemistry or size-dependent mechanisms (Ren et al., 2018; Wang et al., 2018; Xie et al., 2020; Muhammad et al., 2022). Iron-based nanoparticles have been developed for the detection of autophagy (Zhang et al., 2018) and modulating the activity of the lysosome and ALP. Shen et al. (2020) showed that Fe_3O_4 magnetic nanoparticles (Fe_3O_4-NPs) could regulate reactive oxygen radicals and inhibit the hyperphosphorylation of mTOR caused by *Salmonella* Enteritidis infection to alleviate *Salmonella* infection in chicken liver. Albuminuria is a major characteristic of patients with chronic kidney disease and is also a crucial factor in the development of tubulointerstitial fibrosis. Liu et al. (2021) reported that Fe_3O_4 magnetic albumin nanoparticles (Fe_3O_4@BSA) could reverse cationic bovine serum albumin (BSA)-induced kidney damage via rescuing matrix metallopeptidase 2 (MMP2) activity, restoring autophagy flux, and alleviating tubular damage.

4.3.4 Zinc oxide nanoparticles

After cellular internalization of ZnO nanoparticles, the zinc ion release in the lysosome-related acidic compartment prompted the generation of cytotoxic ROS (Cho et al., 2011; Zhang et al., 2017; Kim et al., 2023). ZnO nanoparticles, exhibiting selective toxicity against tumor cells, have also been studied as a potential therapeutic agent for cancer. In addition to the transformation of ZnO nanoparticles upon internalization into lysosome-related organelles, the nanoparticles themselves could also modulate lysosome-related molecular events. Popp and Segatori (2019) assessed the impact of ZnO nanoparticles with differential sizes or surface coatings on the ALP and found that all of them contributed to the activation of the TFEB signaling pathway. However, only naked and triethoxycaprylylsilane-coated nano-ZnO could enhance the formation and turnover of autophagosomes and facilitate the intracellular clearance of lipofuscin in fibroblasts derived from patients with late-infantile neuronal ceroid lipofuscinosis. Additionally, Pei et al.

(2023) reported that ZnO nanoparticles could induce TFEB-regulated autophagy and pyroptosis in hepatocytes, and TFEB-regulated autophagy-lysosomal and lysosomal systems mitigate the pyroptosis induced by ZnO nanoparticles in hepatocytes. Collectively, the surface modification and size of ZnO nanoparticles may affect their regulation of the lysosome/ALP, which provides an important insight for the future design of nano- and micro-sized ZnO materials with expected lysosomal or autophagic regulatory properties.

4.3.5 Europium hydroxide nanorods

Materials contain the rare earth element europium, which exhibits the capability to promote osteogenesis, vascularization, neural regeneration, or antibiosis, highlighting their potential in tissue engineering and regenerative medicine (Wu et al., 2023). Wei et al. (2014, 2015) illustrated that europium hydroxide nanorods could clear mutant huntingtin proteins expressed in neuroblastoma-2A (Neuro-2A) or PC-12 cells by inducing autophagy independent of the protein kinase B (AKT)-mTOR and AMPK signaling pathways. Functionally sound lysosomes and ALP are essential for the clearance of aggregated proteins. Our further investigations suggested that europium hydroxide nanorods could enhance lysosome acidity without disrupting the biosynthesis and integrity of the lysosome. Furthermore, these europium hydroxide nanorods could promote the maturation of the lysosomal hydrolase cathepsin D. In summary, europium hydroxide nanorods not only induced cellular autophagy but also enhanced lysosome acidity, degradation capability, and the fusion of autophagosomes with lysosomes, which provided a strategy for the development of treatments for various neurodegenerative diseases using nanomedicine methods.

5 Concluding remarks and future directions

The dysfunction of lysosomes and ALP is one of the pivotal driving forces of neurodegenerative diseases, metabolic diseases, inflammation, and other related diseases, affecting their onset and progression. Restoring the function of lysosomes or ALP has represented an increasingly important therapeutic strategy in disease management. Herein, we briefly introduced the structure, function, and biogenesis of lysosomes and the ALP. Various diseases, including neurodegenerative diseases, NAFLD, and atherosclerosis, which are closely related to lysosomal/autophagic dysfunction, were also reviewed, emphasizing the significance of restoring lysosomal acidification or regulating ALP function for disease treatment. Finally, we focused on engineered nanomaterials that can restore the function of the lysosome or ALP and summarized different strategies and methods for achieving this goal.

In most cases, organic or inorganic nanomaterials internalized into cells usually tend to localize to lysosome-related acidic organelles, providing a crucial prerequisite for utilizing nanomaterials to regulate the function of lysosomes and restore autophagy flux. The materials studied systematically that can restore lysosomal acidification and degradation ability are mainly acidic nanoparticles, which include PLGA- or PLA-based nanoparticles, succinate-based polymeric nanoparticles, and acidic nucleolipid NEs. Acidic nanomaterials usually contain stimuli-responsive and biodegradable covalent linkages. Upon effective degradation in lysosomes, they can release the acidic functional groups and restore the lysosomal pH. Inorganic nanoparticles, including AuNPs, nanoceria, ZnO nanoparticles, and others, have been reported to enhance the activity of lysosomes and/or ALP. TFEB, a key transcription factor regulating the transcription of genes related to the ALP, is the elemental regulatory mechanism by which metal-based nanomaterials modulate lysosomal activity and ALP activity.

When considering the currently developed materials, it is crucial to determine the suitability of partial or complete design strategies for specific applications. To ensure that any alterations in cellular function are solely attributed to changes in lysosomal pH, meticulous experimental design with appropriate controls is of utmost importance. This can be achieved by incorporating the lysosomal V-ATPase inhibitor bafilomycin A1 and the lysosomal protease inhibitor aloxistatin (E64d) as control measures. Given that lysosomal function also impacts other cellular organelles such as mitochondria, evaluating their functionality alongside changes in lysosomal function would be prudent. Furthermore, assessing the efficacy and pharmacokinetic/pharmacodynamic parameters of these materials or formulations in preclinical models is essential for translational research. By implementing rigorous experimental controls and designs, we aim to enhance our

understanding of how lysosomal pH influences downstream cellular processes and gain valuable insights into optimizing drugs that regulate lysosomal acidification to restore cellular function. This review is intended to elucidate the latest progress in the field of nanomedicine for lysosomal/autophagic defect-related diseases and inspire the development of innovative and clinically valuable nanomedicines.

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Author contributions

Xiaodan HUANG, Yue FANG, and Jie SONG were involved in the investigation, writing – original draft, and visualization. Yuanjing HAO and Yuanyuan CAI were involved in the investigation, writing – original draft, and visualization. Pengfei WEI and Na ZHANG were involved in the conceptualization, writing – review and editing, and supervision. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Xiaodan HUANG, Yue FANG, Jie SONG, Yuanjing HAO, Yuanyuan CAI, Pengfei WEI, and Na ZHANG declare that they have no conflicts of interest.

This review does not include any research with human or animal subjects performed by any of the authors.

References

Abokyi S, Ghartey-Kwansah G, Tse DYY, 2023. TFEB is a central regulator of the aging process and age-related diseases. *Ageing Res Rev*, 89:101985. https://doi.org/10.1016/j.arr.2023.101985

Ahmadi A, Argulian E, Leipsic J, et al., 2019. From subclinical atherosclerosis to plaque progression and acute coronary events: *JACC* state-of-the-art review. *J Am Coll Cardiol*, 74(12):1608-1617. https://doi.org/10.1016/j.jacc.2019.08.012

Aman Y, Schmauck-Medina T, Hansen M, et al., 2021. Autophagy in healthy aging and disease. *Nat Aging*, 1:634-650. https://doi.org/10.1038/s43587-021-00098-4

Anderson JM, Shive MS, 1997. Biodegradation and biocompatibility of PLA and PLGA microspheres. *Adv Drug Delivery Rev*, 28:5-24. https://doi.org/10.1016/s0169-409x(97)00048-3

Antonucci L, Fagman JB, Kim JY, et al., 2015. Basal autophagy maintains pancreatic acinar cell homeostasis and protein synthesis and prevents ER stress. *Proc Natl Acad Sci USA*, 112(45):E6166-E6174. https://doi.org/10.1073/pnas.1519384112

Ardan T, Baxa M, Levinská B, et al., 2020. Transgenic minipig model of Huntington's disease exhibiting gradually progressing neurodegeneration. *Dis Models Mech*, 13(2): dmm041319. https://doi.org/10.1242/dmm.041319

Arotcarena ML, Soria FN, Cunha A, et al., 2022. Acidic nanoparticles protect against α-synuclein-induced neurodegeneration through the restoration of lysosomal function. *Aging Cell*, 21(4):e13584. https://doi.org/10.1111/acel.13584

Assali EA, Shlomo D, Zeng JJ, et al., 2019. Nanoparticle-mediated lysosomal reacidification restores mitochondrial turnover and function in β cells under lipotoxicity. *FASEB J*, 33(3):4154-4165. https://doi.org/10.1096/fj.201801292R

Ayyildiz D, Bergonzoni G, Monziani A, et al., 2023. CAG repeat expansion in the Huntington's disease gene shapes linear and circular RNAs biogenesis. *PLoS Genet*, 19(10): e1010988. https://doi.org/10.1371/journal.pgen.1010988

Bagshaw RD, Mahuran DJ, Callahan JW, 2005. A proteomic analysis of lysosomal integral membrane proteins reveals the diverse composition of the organelle. *Mol Cell Proteomics*, 4(2):133-143. https://doi.org/10.1074/mcp.M400128-MCP200

Ballabio A, Bonifacino JS, 2020. Lysosomes as dynamic regulators of cell and organismal homeostasis. *Nat Rev Mol Cell Biol*, 21(2):101-118. https://doi.org/10.1038/s41580-019-0185-4

Baltazar GC, Guha S, Lu WN, et al., 2012. Acidic nanoparticles are trafficked to lysosomes and restore an acidic lysosomal pH and degradative function to compromised ARPE-19 cells. *PLoS ONE*, 7(12):e49635. https://doi.org/10.1371/journal.pone.0049635

Ben-Shlomo Y, Darweesh S, Llibre-Guerra J, et al., 2024. The epidemiology of Parkinson's disease. *Lancet*, 403(10423): 283-292. https://doi.org/10.1016/S0140-6736(23)01419-8

Bourdenx M, Daniel J, Genin E, et al., 2016. Nanoparticles restore lysosomal acidification defects: implications for Parkinson and other lysosomal-related diseases. *Autophagy*, 12(3):472-483. https://doi.org/10.1080/15548627.2015.1136769

Boya P, 2012. Lysosomal function and dysfunction: mechanism and disease. *Antioxid Redox Signaling*, 17(5):766-774. https://doi.org/10.1089/ars.2011.4405

Braulke T, Carette JE, Palm W, 2024. Lysosomal enzyme trafficking: from molecular mechanisms to human diseases. *Trends Cell Biol*, 34(3):198-210.

https://doi.org/10.1016/j.tcb.2023.06.005

Brouillard M, Barthélémy P, Dehay B, et al., 2021. Nucleolipid acid-based nanocarriers restore neuronal lysosomal acidification defects. *Front Chem*, 9:736554. https://doi.org/10.3389/fchem.2021.736554

Brouillard M, Kinet R, Joyeux M, et al., 2023. Modulating lysosomal pH through innovative multimerized succinic acid-based nucleolipid derivatives. *Bioconjugate Chem*, 34(3): 572-580. https://doi.org/10.1021/acs.bioconjchem.3c00041

Bruijn LI, Houseweart MK, Kato S, et al., 1998. Aggregation and motor neuron toxicity of an ALS-linked SOD1 mutant independent from wild-type SOD1. *Science*, 281(5384): 1851-1854. https://doi.org/10.1126/science.281.5384.1851

Cai XS, She MQ, Xu MY, et al., 2018. GLP-1 treatment protects endothelial cells from oxidative stress-induced autophagy and endothelial dysfunction. *Int J Biol Sci*, 14(12): 1696-1708. https://doi.org/10.7150/ijbs.27774

Calabresi P, di Lazzaro G, Marino G, et al., 2023. Advances in understanding the function of alpha-synuclein: implications for Parkinson's disease. *Brain*, 146(9):3587-3597. https://doi.org/10.1093/brain/awad150

Carlsson SR, Fukuda M, 1992. The lysosomal membrane glycoprotein lamp-1 is transported to lysosomes by two alternative pathways. *Arch Biochem Biophys*, 296(2):630-639. https://doi.org/10.1016/0003-9861(92)90619-8

Ceccariglia S, Cargnoni A, Silini AR, et al., 2020. Autophagy: a potential key contributor to the therapeutic action of mesenchymal stem cells. *Autophagy*, 16(1):28-37. https://doi.org/10.1080/15548627.2019.1630223

Chapel A, Kieffer-Jaquinod S, Sagné C, et al., 2013. An extended proteome map of the lysosomal membrane reveals novel potential transporters. *Mol Cell Proteomics*, 12(6): 1572-1588. https://doi.org/10.1074/mcp.M112.021980

Chattopadhyay M, Valentine JS, 2009. Aggregation of copper–zinc superoxide dismutase in familial and sporadic ALS. *Antioxid Redox Signaling*, 11(7):1603-1614. https://doi.org/10.1089/ars.2009.2536

Chen HY, Ye TW, Hu FQ, et al., 2023. Urchin-like ceria nanoparticles for enhanced gene therapy of osteoarthritis. *Sci Adv*, 9(24):eadf0988. https://doi.org/10.1126/sciadv.adf0988

Chen S, Zhang XJ, Song L, et al., 2012. Autophagy dysregulation in amyotrophic lateral sclerosis. *Brain Pathol*, 22: 110-116. https://doi.org/10.1111/j.1750-3639.2011.00546.x

Chen X, Pandit S, Shi L, et al., 2023. Graphene oxide attenuates toxicity of amyloid-β aggregates in yeast by promoting disassembly and boosting cellular stress response. *Adv Funct Mater*, 33(45):2304053. https://doi.org/10.1002/adfm.202304053

Chen YK, Zeng A, He SM, et al., 2021. Autophagy-related genes in atherosclerosis. *J Healthc Eng*, 2021:6402206. https://doi.org/10.1155/2021/6402206

Chithrani BD, Chan WCW, 2007. Elucidating the mechanism of cellular uptake and removal of protein-coated gold nanoparticles of different sizes and shapes. *Nano Lett*, 7(6):1542-1550. https://doi.org/10.1021/nl070363y

Chithrani BD, Ghazani AA, Chan WCW, 2006. Determining the size and shape dependence of gold nanoparticle uptake into mammalian cells. *Nano Lett*, 6(4):662-668. https://doi.org/10.1021/nl052396o

Cho WS, Duffin R, Howie SEM, et al., 2011. Progressive severe lung injury by zinc oxide nanoparticles; the role of Zn^{2+} dissolution inside lysosomes. *Part Fibre Toxicol*, 8:27. https://doi.org/10.1186/1743-8977-8-27

Choi I, Wang MH, Yoo S, et al., 2023. Autophagy enables microglia to engage amyloid plaques and prevents microglial senescence. *Nat Cell Biol*, 25(7):963-974. https://doi.org/10.1038/s41556-023-01158-0

Chu FX, Li K, Li XL, et al., 2021. Graphene oxide ameliorates the cognitive impairment through inhibiting PI3K/Akt/mTOR pathway to induce autophagy in AD mouse model. *Neurochem Res*, 46(2):309-325. https://doi.org/10.1007/s11064-020-03167-z

Cunha A, Prévot G, Mousli Y, et al., 2020. Synthesis and intracellular uptake of rhodamine–nucleolipid conjugates into a nanoemulsion vehicle. *ACS Omega*, 5(11):5815-5823. https://doi.org/10.1021/acsomega.9b03992

dal Canto MC, Gurney ME, 1995. Neuropathological changes in two lines of mice carrying a transgene for mutant human Cu, Zn SOD, and in mice overexpressing wild type human SOD: a model of familial amyotrophic lateral sclerosis (FALS). *Brain Res*, 676:25-40. https://doi.org/10.1016/0006-8993(95)00063-v

Davoody S, Taei AA, Khodabakhsh P, et al., 2024. mTOR signaling and Alzheimer's disease: what we know and where we are? *CNS Neurosci Ther*, 30(4):e14463. https://doi.org/10.1111/cns.14463

Dehay B, Bové J, Rodríguez-Muela N, et al., 2010. Pathogenic lysosomal depletion in Parkinson's disease. *J Neurosci*, 30(37):12535-12544. https://doi.org/10.1523/jneurosci.1920-10.2010

Devadiga SJ, Bharate SS, 2022. Recent developments in the management of Huntington's disease. *Bioorg Chem*, 120: 105642. https://doi.org/10.1016/j.bioorg.2022.105642

Diakopoulos KN, Lesina M, Wörmann S, et al., 2015. Impaired autophagy induces chronic atrophic pancreatitis in mice via sex-and nutrition-dependent processes. *Gastroenterology*, 148(3):626-638.e17. https://doi.org/10.1053/j.gastro.2014.12.003

Dikic I, Elazar Z, 2018. Mechanism and medical implications of mammalian autophagy. *Nat Rev Mol Cell Biol*, 19(6): 349-364. https://doi.org/10.1038/s41580-018-0003-4

Eskelinen EL, 2006. Roles of LAMP-1 and LAMP-2 in lysosome biogenesis and autophagy. *Mol Aspects Med*, 27(5-6): 495-502. https://doi.org/10.1016/j.mam.2006.08.005

Ezquerro S, Mocha F, Frühbeck G, et al., 2019. Ghrelin reduces TNF-α-induced human hepatocyte apoptosis, autophagy, and pyroptosis: role in obesity-associated NAFLD. *J Clin Endocrinol Metab*, 104(1):21-37. https://doi.org/10.1210/jc.2018-01171

Fang EF, Scheibye-Knudsen M, Brace LE, et al., 2014. Defective mitophagy in XPA via PARP-1 hyperactivation and NAD^+/SIRT1 reduction. *Cell*, 157(4):882-896. https://doi.org/10.1016/j.cell.2014.03.026

Fang EF, Kassahun H, Croteau DL, et al., 2016. NAD^+ replenishment improves lifespan and healthspan in ataxia telangiectasia models via mitophagy and DNA repair. *Cell Metab*, 24(4):566-581. https://doi.org/10.1016/j.cmet.2016.09.004

Fang EF, Hou YJ, Palikaras K, et al., 2019. Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. *Nat Neurosci*, 22(3):401-412. https://doi.org/10.1038/s41593-018-0332-9

Fang EF, Xie CL, Schenkel JA, et al., 2020. A research agenda for ageing in China in the 21st century (2nd edition): focusing on basic and translational research, long-term care, policy and social networks. *Ageing Res Rev*, 64:101174. https://doi.org/10.1016/j.arr.2020.101174

Feldman EL, Goutman SA, Petri S, et al., 2022. Amyotrophic lateral sclerosis. *Lancet*, 400(10360):1363-1380. https://doi.org/10.1016/s0140-6736(22)01272-7

Frendo-Cumbo S, Tokarz VL, Bilan PJ, et al., 2021. Communication between autophagy and insulin action: at the crux of insulin action-insulin resistance? *Front Cell Dev Biol*, 9:708431. https://doi.org/10.3389/fcell.2021.708431

Fukuo Y, Yamashina S, Sonoue H, et al., 2014. Abnormality of autophagic function and cathepsin expression in the liver from patients with non-alcoholic fatty liver disease. *Hepatol Res*, 44(9):1026-1036. https://doi.org/10.1111/hepr.12282

Ge PP, Gao MX, Du J, et al., 2021. Downregulation of microRNA-512-3p enhances the viability and suppresses the apoptosis of vascular endothelial cells, alleviates autophagy and endoplasmic reticulum stress as well as represses atherosclerotic lesions in atherosclerosis by adjusting spliced/unspliced ratio of X-box binding protein 1 (XBP-1S/XBP-1U). *Bioengineered*, 12(2):12469-12481. https://doi.org/10.1080/21655979.2021.2006862

Ghazali SAISM, Fatimah I, Zamil ZN, et al., 2023. Graphene quantum dots: a comprehensive overview. *Open Chem*, 21:20220285. https://doi.org/10.1515/chem-2022-0285

Gissot A, Camplo M, Grinstaff MW, et al., 2008. Nucleoside, nucleotide and oligonucleotide based amphiphiles: a successful marriage of nucleic acids with lipids. *Org Biomol Chem*, 6(8):1324-1333. https://doi.org/10.1039/b719280k

Griffey CJ, Yamamoto A, 2022. Macroautophagy in CNS health and disease. *Nat Rev Neurosci*, 23(7):411-427. https://doi.org/10.1038/s41583-022-00588-3

Gros F, Muller S, 2023. The role of lysosomes in metabolic and autoimmune diseases. *Nat Rev Nephrol*, 19(6):366-383. https://doi.org/10.1038/s41581-023-00692-2

Gukovskaya AS, Gukovsky I, 2012. Autophagy and pancreatitis. *Am J Physiol-Gastrointest Liver Physiol*, 303(9):G993-G1003. https://doi.org/10.1152/ajpgi.00122.2012

Guo YL, Duan WJ, Lu DH, et al., 2021. Autophagy-dependent removal of α-synuclein: a novel mechanism of GM1 ganglioside neuroprotection against Parkinson's disease. *Acta Pharmacol Sin*, 42(4):518-528. https://doi.org/10.1038/s41401-020-0454-y

Hämälistö S, Jäättelä M, 2016. Lysosomes in cancer—living on the edge (of the cell). *Curr Opin Cell Biol*, 39:69-76. https://doi.org/10.1016/j.ceb.2016.02.009

Hamburg NM, Creager MA, 2017. Pathophysiology of intermittent claudication in peripheral artery disease. *Circ J*, 81(3):281-289. https://doi.org/10.1253/circj.CJ-16-1286

He JL, Liu JY, Huang Y, et al., 2021. Oxidative stress, inflammation, and autophagy: potential targets of mesenchymal stem cells-based therapies in ischemic stroke. *Front Neurosci*, 15:641157. https://doi.org/10.3389/fnins.2021.641157

He LN, Zhao JT, Wang LM, et al., 2021. Using nano-selenium to combat coronavirus disease 2019 (COVID-19)? *Nano Today*, 36:101037. https://doi.org/10.1016/j.nantod.2020.101037

He LZ, Huang GN, Liu HX, et al., 2020. Highly bioactive zeolitic imidazolate framework-8–capped nanotherapeutics for efficient reversal of reperfusion-induced injury in ischemic stroke. *Sci Adv*, 6(12):eaay9751. https://doi.org/10.1126/sciadv.aay9751

Herrington W, Lacey B, Sherliker P, et al., 2016. Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. *Circ Res*, 118(4):535-546. https://doi.org/10.1161/circresaha.115.307611

Holland LKK, Nielsen IØ, Maeda K, et al., 2020. Snapshot: lysosomal functions. *Cell*, 181(3):748-748.e1. https://doi.org/10.1016/j.cell.2020.03.043

Hong SE, An JH, Yu SL, et al., 2020. Ceria-zirconia antioxidant nanoparticles attenuate hypoxia-induced acute kidney injury by restoring autophagy flux and alleviating mitochondrial damage. *J Biomed Nanotechnol*, 16(7):1144-1159. https://doi.org/10.1166/jbn.2020.2948

Howe CL, Granger BL, Hull M, et al., 1988. Derived protein sequence, oligosaccharides, and membrane insertion of the 120-kDa lysosomal membrane glycoprotein (lgp120): identification of a highly conserved family of lysosomal membrane glycoproteins. *Proc Natl Acad Sci USA*, 85(20):7577-7581. https://doi.org/10.1073/pnas.85.20.7577

Hu L, Liu Y, Wang S, 2018. Stem cell-based tooth and periodontal regeneration. *Oral Dis*, 24(5):696-705. https://doi.org/10.1111/odi.12703

Hu XD, Lin R, Zhang CQ, et al., 2023. Nano-selenium alleviates cadmium-induced mouse leydig cell injury, via the inhibition of reactive oxygen species and the restoration of autophagic flux. *Reprod Sci*, 30(6):1808-1822. https://doi.org/10.1007/s43032-022-01146-z

Huang YY, Yu MX, Zheng J, 2023. Proximal tubules eliminate endocytosed gold nanoparticles through an organelle-extrusion-mediated self-renewal mechanism. *Nat Nanotechnol*, 18(6):637-646. https://doi.org/10.1038/s41565-023-01366-7

Ilieva H, Vullaganti M, Kwan J, 2023. Advances in molecular pathology, diagnosis, and treatment of amyotrophic lateral sclerosis. *BMJ*, 383:e075037. https://doi.org/10.1136/bmj-2023-075037

Inami Y, Yamashina S, Izumi K, et al., 2011. Hepatic steatosis inhibits autophagic proteolysis via impairment of autophagosomal acidification and cathepsin expression. *Biochem Biophys Res Commun*, 412(4):618-625. https://doi.org/10.1016/j.bbrc.2011.08.012

Iyaswamy A, Thakur A, Guan XJ, et al., 2023. Fe65-engineered neuronal exosomes encapsulating corynoxine-B ameliorate cognition and pathology of Alzheimer's disease. *Signal Transduct Target Ther*, 8:404. https://doi.org/10.1038/s41392-023-01657-4

Janvier K, Bonifacino JS, 2005. Role of the endocytic machinery in the sorting of lysosome-associated membrane proteins. *Mol Biol Cell*, 16(9):4231-4242. https://doi.org/10.1091/mbc.e05-03-0213

Jeong JK, Lee YJ, Jeong SY, et al., 2017. Autophagic flux induced by graphene oxide has a neuroprotective effect against human prion protein fragments. *Int J Nanomed*, 12:8143-8158. https://doi.org/10.2147/ijn.S146398

Jerome WG, Cox BE, Griffin EE, et al., 2008. Lysosomal cholesterol accumulation inhibits subsequent hydrolysis of lipoprotein cholesteryl ester. *Microsc Microanal*, 14(2):138-149. https://doi.org/10.1017/s1431927608080069

Jin PP, Wei PF, Zhang YJ, et al., 2016. Autophagy-mediated clearance of ubiquitinated mutant huntingtin by graphene oxide. *Nanoscale*, 8(44):18740-18750. https://doi.org/10.1039/c6nr07255k

Johnson AA, Cuellar TL, 2023. Glycine and aging: evidence and mechanisms. *Ageing Res Rev*, 87:101922. https://doi.org/10.1016/j.arr.2023.101922

Kang I, Yoo JM, Kim D, et al., 2021. Graphene quantum dots alleviate impaired functions in Niemann-Pick disease type C in vivo. *Nano Lett*, 21(5):2339-2346. https://doi.org/10.1021/acs.nanolett.0c03741

Kashima J, Shintani-Ishida K, Nakajima M, et al., 2014. Immunohistochemical study of the autophagy marker microtubule-associated protein 1 light chain 3 in normal and steatotic human livers. *Hepatol Res*, 44(7):779-787. https://doi.org/10.1111/hepr.12183

Kaur SJ, McKeown SR, Rashid S, 2016. Mutant SOD1 mediated pathogenesis of amyotrophic lateral sclerosis. *Gene*, 577(2):109-118. https://doi.org/10.1016/j.gene.2015.11.049

Kegel KB, Kim M, Sapp E, et al., 2000. Huntingtin expression stimulates endosomal–lysosomal activity, endosome tubulation, and autophagy. *J Neurosci*, 20(19):7268-7278. https://doi.org/10.1523/jneurosci.20-19-07268.2000

Kim B, Kim G, Jeon S, et al., 2023. Zinc oxide nanoparticles trigger autophagy-mediated cell death through activating lysosomal TRPML1 in normal kidney cells. *Toxicol Rep*, 10:529-536. https://doi.org/10.1016/j.toxrep.2023.04.012

Kim D, Yoo JM, Hwang H, et al., 2018. Graphene quantum dots prevent α-synucleinopathy in Parkinson's disease. *Nat Nanotechnol*, 13(9):812-818. https://doi.org/10.1038/s41565-018-0179-y

Kim YG, Lee Y, Lee N, et al., 2024. Ceria-based therapeutic antioxidants for biomedical applications. *Adv Mater*, 36(10):2210819. https://doi.org/10.1002/adma.202210819

Koga H, Kaushik S, Cuervo AM, 2010. Altered lipid content inhibits autophagic vesicular fusion. *FASEB J*, 24(8):3052-3065. https://doi.org/10.1096/fj.09-144519

Koleini N, Kardami E, 2017. Autophagy and mitophagy in the context of doxorubicin-induced cardiotoxicity. *Oncotarget*, 8(28):46663-46680. https://doi.org/10.18632/oncotarget.16944

Kornfeld S, Mellman I, 1989. The biogenesis of lysosomes. *Ann Rev Cell Biol*, 5:483-525. https://doi.org/10.1146/annurev.cb.05.110189.002411

Krach F, Stemick J, Boerstler T, et al., 2022. An alternative splicing modulator decreases mutant HTT and improves the molecular fingerprint in Huntington's disease patient neurons. *Nat Commun*, 13:6797. https://doi.org/10.1038/s41467-022-34419-x

Kumari A, Yadav SK, Yadav SC, 2010. Biodegradable polymeric nanoparticles based drug delivery systems. *Colloids Surf B Biointerfaces*, 75:1-18. https://doi.org/10.1016/j.colsurfb.2009.09.001

Kyle S, Saha S, 2014. Nanotechnology for the detection and therapy of stroke. *Adv Healthcare Mater*, 3(11):1703-1720. https://doi.org/10.1002/adhm.201400009

Labrijn AF, Meesters JI, Bunce M, et al., 2017. Efficient generation of bispecific murine antibodies for pre-clinical investigations in syngeneic rodent models. *Sci Rep*, 7:2476. https://doi.org/10.1038/s41598-017-02823-9

Las G, Serada SB, Wikstrom JD, et al., 2011. Fatty acids suppress autophagic turnover in β-cells. *J Biol Chem*, 286(49):42534-42544. https://doi.org/10.1074/jbc.M111.242412

Lebeaupin C, Vallée D, Hazari Y, et al., 2018. Endoplasmic reticulum stress signalling and the pathogenesis of non-alcoholic fatty liver disease. *J Hepatol*, 69(4):927-947. https://doi.org/10.1016/j.jhep.2018.06.008

Lee J, Sung KW, Bae EJ, et al., 2023. Targeted degradation of α-synuclein aggregates in Parkinson's disease using the AUTOTAC technology. *Mol Neurodegener*, 18:41. https://doi.org/10.1186/s13024-023-00630-7

Lee JH, Nixon RA, 2022. Autolysosomal acidification failure as a primary driver of Alzheimer disease pathogenesis. *Autophagy*, 18(11):2763-2764. https://doi.org/10.1080/15548627.2022.2110729

Lee JH, Yang DS, Goulbourne CN, et al., 2022. Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of Aβ in neurons, yielding senile plaques. *Nat Neurosci*, 25(6):688-701. https://doi.org/10.1038/s41593-022-01084-8

Leidal AM, Levine B, Debnath J, 2018. Autophagy and the cell biology of age-related disease. *Nat Cell Biol*, 20(12): 1338-1348. https://doi.org/10.1038/s41556-018-0235-8

Lescat L, Herpin A, Mourot B, et al., 2018. CMA restricted to mammals and birds: myth or reality? *Autophagy*, 14(7): 1267-1270. https://doi.org/10.1080/15548627.2018.1460021

Levine B, Kroemer G, 2019. Biological functions of autophagy genes: a disease perspective. *Cell*, 176(1-2):11-42. https://doi.org/10.1016/j.cell.2018.09.048

Li DL, Wang ZV, Ding GQ, et al., 2016. Doxorubicin blocks cardiomyocyte autophagic flux by inhibiting lysosome acidification. *Circulation*, 133(17):1668-1687. https://doi.org/10.1161/circulationaha.115.017443

Li MC, Sala V, de Santis MC, et al., 2018. Phosphoinositide 3-kinase gamma inhibition protects from anthracycline cardiotoxicity and reduces tumor growth. *Circulation*, 138(7):696-711. https://doi.org/10.1161/circulationaha.117.030352

Li Q, Yang GW, Li JL, et al., 2020. Stem cell therapies for periodontal tissue regeneration: a network meta-analysis of preclinical studies. *Stem Cell Res Ther*, 11:427. https://doi.org/10.1186/s13287-020-01938-7

Li SL, Zhang CQ, Cao WP, et al., 2015. Anchoring effects of surface chemistry on gold nanorods: modulating autophagy. *J Mater Chem B*, 3(16):3324-3330. https://doi.org/10.1039/c5tb00076a

Li XL, Li K, Chu FX, et al., 2020. Graphene oxide enhances β-amyloid clearance by inducing autophagy of microglia and neurons. *Chem-Biol Interact*, 325:109126. https://doi.org/10.1016/j.cbi.2020.109126

Li ZY, Wang C, Wang ZY, et al., 2019. Allele-selective lowering of mutant HTT protein by HTT–LC3 linker compounds. *Nature*, 575:203-209. https://doi.org/10.1038/s41586-019-1722-1

Lin L, Zhang MX, Zhang L, et al., 2022. Autophagy, pyroptosis, and ferroptosis: new regulatory mechanisms for atherosclerosis. *Front Cell Dev Biol*, 9:809955. https://doi.org/10.3389/fcell.2021.809955

Litwiniuk A, Juszczak GR, Stankiewicz AM, et al., 2023. The role of glial autophagy in Alzheimer's disease. *Mol Psychiatry*, 28(11):4528-4539. https://doi.org/10.1038/s41380-023-02242-5

Liu HY, Han JM, Cao SY, et al., 2009. Hepatic autophagy is suppressed in the presence of insulin resistance and hyperinsulinemia. *J Biol Chem*, 284(45):31484-31492. https://doi.org/10.1074/jbc.M109.033936

Liu L, Xu Q, Zhang L, et al., 2021. Fe_3O_4 magnetic nanoparticles ameliorate albumin-induced tubulointerstitial fibrosis by autophagy related to Rab7. *Colloids Surf B Biointerfaces*, 198:111470. https://doi.org/10.1016/j.colsurfb.2020.111470

Liu W, Wang G, Wang ZW, et al., 2022. Repurposing small-molecule drugs for modulating toxic protein aggregates in neurodegenerative diseases. *Drug Discovery Today*, 27(7):1994-2007. https://doi.org/10.1016/j.drudis.2022.04.003

Liu Y, Wang XN, Wang J, et al., 2016. Graphene oxide attenuates the cytotoxicity and mutagenicity of PCB 52 via activation of genuine autophagy. *Environ Sci Technol*, 50(6): 3154-3164. https://doi.org/10.1021/acs.est.5b03895

López-Otín C, Blasco MA, Partridge L, et al., 2023. Hallmarks of aging: an expanding universe. *Cell*, 186(2):243-278. https://doi.org/10.1016/j.cell.2022.11.001

Lou GF, Palikaras K, Lautrup S, et al., 2020. Mitophagy and neuroprotection. *Trends Mol Med*, 26(1):8-20. https://doi.org/10.1016/j.molmed.2019.07.002

Ma NN, Liu PD, He NY, et al., 2017. Action of gold nanospikes-based nanoradiosensitizers: cellular internalization, radiotherapy, and autophagy. *ACS Appl Mater Interfaces*, 9(37):31526-31542. https://doi.org/10.1021/acsami.7b09599

Ma XW, Wu YY, Jin SB, et al., 2011. Gold nanoparticles induce autophagosome accumulation through size-dependent nanoparticle uptake and lysosome impairment. *ACS Nano*, 5(11):8629-8639. https://doi.org/10.1021/nn202155y

Mahapatro A, Singh DK, 2011. Biodegradable nanoparticles are excellent vehicle for site directed *in-vivo* delivery of drugs and vaccines. *J Nanobiotechnol*, 9:55. https://doi.org/10.1186/1477-3155-9-55

Mahmoudi M, Akhavan O, Ghavami M, et al., 2012. Graphene oxide strongly inhibits amyloid beta fibrillation. *Nanoscale*, 4(23):7322-7325. https://doi.org/10.1039/c2nr31657a

Mak SK, McCormack AL, Manning-Boğ AB, et al., 2010. Lysosomal degradation of α-synuclein *in vivo*. *J Biol Chem*, 285(18):13621-13629. https://doi.org/10.1074/jbc.M109.074617

Mamais A, Wallings R, Rocha EM, 2023. Disease mechanisms as subtypes: lysosomal dysfunction in the endolysosomal Parkinson's disease subtype. *Handb Clin Neurol*, 193:33-51. https://doi.org/10.1016/B978-0-323-85555-6.00009-6

Mareninova OA, Hermann K, French SW, et al., 2009. Impaired autophagic flux mediates acinar cell vacuole formation and trypsinogen activation in rodent models of acute pancreatitis. *J Clin Invest*, 119(11):3340-3355. https://doi.org/10.1172/jci38674

Mareninova OA, Sendler M, Malla SR, et al., 2015. Lysosome-associated membrane proteins (LAMP) maintain pancreatic acinar cell homeostasis: LAMP-2–deficient mice

develop pancreatitis. *Cell Mol Gastroenterol Hepatol*, 1(6): 678-694. https://doi.org/10.1016/j.jcmgh.2015.07.006

Mari M, Bujny MV, Zeuschner D, et al., 2008. SNX1 defines an early endosomal recycling exit for sortilin and mannose 6-phosphate receptors. *Traffic*, 9(3):380-393. https://doi.org/10.1111/j.1600-0854.2007.00686.x

Martens S, Fracchiolla D, 2020. Activation and targeting of ATG8 protein lipidation. *Cell Discov*, 6:23. https://doi.org/10.1038/s41421-020-0155-1

Martina JA, Chen Y, Gucek M, et al., 2012. MTORC1 functions as a transcriptional regulator of autophagy by preventing nuclear transport of TFEB. *Autophagy*, 8(6):903-914. https://doi.org/10.4161/auto.19653

Martinez-Vicente M, Talloczy Z, Wong E, et al., 2010. Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease. *Nat Neurosci*, 13(5):567-576. https://doi.org/10.1038/nn.2528

Mattson MP, Arumugam TV, 2018. Hallmarks of brain aging: adaptive and pathological modification by metabolic states. *Cell Metab*, 27(6):1176-1199. https://doi.org/10.1016/j.cmet.2018.05.011

Maysinger D, Gran ER, Bertorelle F, et al., 2020. Gold nanoclusters elicit homeostatic perturbations in glioblastoma cells and adaptive changes of lysosomes. *Theranostics*, 10(4):1633-1648. https://doi.org/10.7150/thno.37674

McColgan P, Tabrizi SJ, 2018. Huntington's disease: a clinical review. *Eur J Neurol*, 25(1):24-34. https://doi.org/10.1111/ene.13413

Menghini R, Casagrande V, Marino A, et al., 2014. MiR-216a: a link between endothelial dysfunction and autophagy. *Cell Death Dis*, 5:e1029. https://doi.org/10.1038/cddis.2013.556

Miceli C, Leri M, Stefani M, et al., 2023. Autophagy-related proteins: potential diagnostic and prognostic biomarkers of aging-related diseases. *Ageing Res Rev*, 89:101967. https://doi.org/10.1016/j.arr.2023.101967

Mir SUR, George NM, Zahoor L, et al., 2015. Inhibition of autophagic turnover in β-cells by fatty acids and glucose leads to apoptotic cell death. *J Biol Chem*, 290(10):6071-6085. https://doi.org/10.1074/jbc.M114.605345

Mizushima N, Komatsu M, 2011. Autophagy: renovation of cells and tissues. *Cell*, 147(4):728-741. https://doi.org/10.1016/j.cell.2011.10.026

Moore KJ, Sheedy FJ, Fisher EA, 2013. Macrophages in atherosclerosis: a dynamic balance. *Nat Rev Immunol*, 13(10): 709-721. https://doi.org/10.1038/nri3520

Morris HR, Spillantini MG, Sue CM, et al., 2024. The pathogenesis of Parkinson's disease. *Lancet*, 403(10423):293-304. https://doi.org/10.1016/s0140-6736(23)01478-2

Muhammad P, Hanif S, Li JY, et al., 2022. Carbon dots supported single Fe atom nanozyme for drug-resistant glioblastoma therapy by activating autophagy-lysosome pathway. *Nano Today*, 45:101530. https://doi.org/10.1016/j.nantod.2022.101530

Nowell J, Blunt E, Gupta D, et al., 2023. Antidiabetic agents as a novel treatment for Alzheimer's and Parkinson's disease. *Ageing Res Rev*, 89:101979. https://doi.org/10.1016/j.arr.2023.101979

Pan L, Feigin A, 2021. Huntington's disease: new frontiers in therapeutics. *Curr Neurol Neurosci Rep*, 21(3):10. https://doi.org/10.1007/s11910-021-01093-3

Partridge L, Deelen J, Slagboom PE, 2018. Facing up to the global challenges of ageing. *Nature*, 561:45-56. https://doi.org/10.1038/s41586-018-0457-8

Parzych KR, Klionsky DJ, 2014. An overview of autophagy: morphology, mechanism, and regulation. *Antioxid Redox Signaling*, 20(3):460-473. https://doi.org/10.1089/ars.2013.5371

Payne T, Burgess T, Bradley S, et al., 2024. Multimodal assessment of mitochondrial function in Parkinson's disease. *Brain*, 147(1):267-280. https://doi.org/10.1093/brain/awad364

Pei XY, Liu DK, Li JJ, et al., 2023. TFEB coordinates autophagy and pyroptosis as hepatotoxicity responses to ZnO nanoparticles. *Sci Total Environ*, 865:161242. https://doi.org/10.1016/j.scitotenv.2022.161242

Peshkova IO, Schaefer G, Koltsova EK, 2016. Atherosclerosis and aortic aneurysm – is inflammation a common denominator? *FEBS J*, 283(9):1636-1652. https://doi.org/10.1111/febs.13634

Piras A, Collin L, Grüninger F, et al., 2016. Autophagic and lysosomal defects in human tauopathies: analysis of postmortem brain from patients with familial Alzheimer disease, corticobasal degeneration and progressive supranuclear palsy. *Acta Neuropathol Commun*, 4:22. https://doi.org/10.1186/s40478-016-0292-9

Popp L, Segatori L, 2019. Zinc oxide particles induce activation of the lysosome–autophagy system. *ACS Omega*, 4(1): 573-581. https://doi.org/10.1021/acsomega.8b01497

Presterud R, Deng WH, Wennerström AB, et al., 2024. Long-term nicotinamide riboside use improves coordination and eye movements in ataxia telangiectasia. *Mov Disord*, 39(2):360-369. https://doi.org/10.1002/mds.29645

Prévot G, Soria FN, Thiolat ML, et al., 2018. Harnessing lysosomal pH through PLGA nanoemulsion as a treatment of lysosomal-related neurodegenerative diseases. *Bioconjugate Chem*, 29(12):4083-4089. https://doi.org/10.1021/acs.bioconjchem.8b00697

Prieto GA, Cotman CW, 2022. Early bioenergetic and autophagy impairments at the Parkinson's disease synapse. *Brain*, 145(6):1877-1879. https://doi.org/10.1093/brain/awac191

Queiroz A, Albuquerque-Souza E, Gasparoni LM, et al., 2021. Therapeutic potential of periodontal ligament stem cells. *World J Stem Cells*, 13(6):605-618. https://doi.org/10.4252/wjsc.v13.i6.605

Ren XQ, Chen YT, Peng HB, et al., 2018. Blocking autophagic

flux enhances iron oxide nanoparticle photothermal therapeutic efficiency in cancer treatment. *ACS Appl Mater Interfaces*, 10(33):27701-27711. https://doi.org/10.1021/acsami.8b10167

Riccardi C, Musumeci D, Irace C, et al., 2017. Ru^{III} complexes for anticancer therapy: the importance of being nucleolipidic. *Eur J Org Chem*, 2017(7):1100-1119. https://doi.org/10.1002/ejoc.201600943

Robberecht W, Philips T, 2013. The changing scene of amyotrophic lateral sclerosis. *Nat Rev Neurosci*, 14(4):248-264. https://doi.org/10.1038/nrn3430

Rubinsztein DC, Gestwicki JE, Murphy LO, et al., 2007. Potential therapeutic applications of autophagy. *Nat Rev Drug Discov*, 6(4):304-312. https://doi.org/10.1038/nrd2272

Saftig P, Klumperman J, 2009. Lysosome biogenesis and lysosomal membrane proteins: trafficking meets function. *Nat Rev Mol Cell Biol*, 10(9):623-635. https://doi.org/10.1038/nrm2745

Santin Y, Formoso K, Haidar F, et al., 2023. Inhalation of acidic nanoparticles prevents doxorubicin cardiotoxicity through improvement of lysosomal function. *Theranostics*, 13(15):5435-5451. https://doi.org/10.7150/thno.86310

Sardiello M, Palmieri M, Di Ronza A, et al., 2009. A gene network regulating lysosomal biogenesis and function. *Science*, 325(5939):473-477. https://doi.org/10.1126/science.1174447

Schmauck-Medina T, Molière A, Lautrup S, et al., 2022. New hallmarks of ageing: a 2022 Copenhagen ageing meeting summary. *Aging*, 14(16):6829-6839. https://doi.org/10.18632/aging.204248

Schützmann MP, Hasecke F, Bachmann S, et al., 2021. Endolysosomal Aβ concentration and pH trigger formation of Aβ oligomers that potently induce Tau missorting. *Nat Commun*, 12:4634. https://doi.org/10.1038/s41467-021-24900-4

Seo BM, Miura M, Gronthos S, et al., 2004. Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet*, 364(9429):149-155. https://doi.org/10.1016/s0140-6736(04)16627-0

Settembre C, Perera RM, 2024. Lysosomes as coordinators of cellular catabolism, metabolic signalling and organ physiology. *Nat Rev Mol Cell Biol*, 25(3):223-245. https://doi.org/10.1038/s41580-023-00676-x

Settembre C, de Cegli R, Mansueto G, et al., 2013. TFEB controls cellular lipid metabolism through a starvation-induced autoregulatory loop. *Nat Cell Biol*, 15(6):647-658. https://doi.org/10.1038/ncb2718

Shao BZ, Han BZ, Zeng YX, et al., 2016. The roles of macrophage autophagy in atherosclerosis. *Acta Pharmacol Sin*, 37(2):150-156. https://doi.org/10.1038/aps.2015.87

Shen YR, Xiao YQ, Zhang S, et al., 2020. Fe_3O_4 nanoparticles attenuated *Salmonella* infection in chicken liver through reactive oxygen and autophagy via PI3K/Akt/mTOR signaling. *Front Physiol*, 10:1580. https://doi.org/10.3389/fphys.2019.01580

Shimobayashi M, Hall MN, 2014. Making new contacts: the mTOR network in metabolism and signalling crosstalk. *Nat Rev Mol Cell Biol*, 15(3):155-162. https://doi.org/10.1038/nrm3757

Simeone L, Mangiapia G, Irace C, et al., 2011. Nucleolipid nanovectors as molecular carriers for potential applications in drug delivery. *Mol BioSyst*, 7(11):3075-3086. https://doi.org/10.1039/c1mb05143a

Song WS, Lee SS, Savini M, et al., 2014. Ceria nanoparticles stabilized by organic surface coatings activate the lysosome-autophagy system and enhance autophagic clearance. *ACS Nano*, 8(10):10328-10342. https://doi.org/10.1021/nn505073u

Sun YN, Li MJ, Zhao DF, et al., 2020. Lysosome activity is modulated by multiple longevity pathways and is important for lifespan extension in *C. elegans. eLife*, 9:e55745. https://doi.org/10.7554/eLife.55745

Swastika, Chaturvedi S, Kaul A, et al., 2019. Evaluation of BBB permeable nucleolipid (NL_{DPU}): a di-C15-ketalised palmitone appended uridine as neuro-tracer for SPECT. *Int J Pharm*, 565:269-282. https://doi.org/10.1016/j.ijpharm.2019.04.074

Tisi A, Flati V, Monache SD, et al., 2020. Nanoceria particles are an eligible candidate to prevent age-related macular degeneration by inhibiting retinal pigment epithelium cell death and autophagy alterations. *Cells*, 9(7):1617. https://doi.org/10.3390/cells9071617

Trudeau KM, Colby AH, Zeng JL, et al., 2016. Lysosome acidification by photoactivated nanoparticles restores autophagy under lipotoxicity. *J Cell Biol*, 214(1):25-34. https://doi.org/10.1083/jcb.201511042

Tu HY, Yuan BS, Hou XO, et al., 2021. α-Synuclein suppresses microglial autophagy and promotes neurodegeneration in a mouse model of Parkinson's disease. *Aging Cell*, 20(12):e13522. https://doi.org/10.1111/acel.13522

Ueno T, Komatsu M, 2017. Autophagy in the liver: functions in health and disease. *Nat Rev Gastroenterol Hepatol*, 14(3):170-184. https://doi.org/10.1038/nrgastro.2016.185

van Tiel FH, Boere WA, Harmsen T, et al., 1985. Determination of inhibitory concentrations of antiviral agents in cell culture by use of an enzyme immunoassay with virus-specific, peroxidase-labeled monoclonal antibodies. *Antimicrob Agents Chemother*, 27(5):802-805. https://doi.org/10.1128/aac.27.5.802

Veverová K, Laczó J, Katonová A, et al., 2024. Alterations of human CSF and serum-based mitophagy biomarkers in the continuum of Alzheimer disease. *Autophagy*, 20(8):1868-1878. https://doi.org/10.1080/15548627.2024.2340408

Wallings RL, Humble SW, Ward ME, et al., 2019. Lysosomal dysfunction at the centre of Parkinson's disease and frontotemporal dementia/amyotrophic lateral sclerosis. *Trends Neurosci*, 42(12):899-912. https://doi.org/10.1016/j.tins.2019.10.002

Wan HY, Chen JL, Zhu XZ, et al., 2018. Titania-coated gold nano-bipyramids for blocking autophagy flux and sensitizing cancer cells to proteasome inhibitor-induced death. *Adv Sci*, 5(3):1700585. https://doi.org/10.1002/advs.201700585

Wang L, Wang ZJ, Li XM, et al., 2018. Deciphering active biocompatibility of iron oxide nanoparticles from their intrinsic antagonism. *Nano Res*, 11(5):2746-2755. https://doi.org/10.1007/s12274-017-1905-8

Wang Q, Wang Y, Li SP, et al., 2023. PACAP–Sirtuin3 alleviates cognitive impairment through autophagy in Alzheimer's disease. *Alzheimers Res Ther*, 15:184. https://doi.org/10.1186/s13195-023-01334-2

Wang Y, Wu Q, Anand BG, et al., 2020. Significance of cytosolic cathepsin D in Alzheimer's disease pathology: protective cellular effects of PLGA nanoparticles against β-amyloid-toxicity. *Neuropathol Appl Neurobiol*, 46(7): 686-706. https://doi.org/10.1111/nan.12647

Wei PF, Zhang L, Nethi SK, et al., 2014. Accelerating the clearance of mutant huntingtin protein aggregates through autophagy induction by europium hydroxide nanorods. *Biomaterials*, 35(3):899-907. https://doi.org/10.1016/j.biomaterials.2013.10.024

Wei PF, Jin PP, Barui AK, et al., 2015. Differential ERK activation during autophagy induced by europium hydroxide nanorods and trehalose: maximum clearance of huntingtin aggregates through combined treatment. *Biomaterials*, 73: 160-174. https://doi.org/10.1016/j.biomaterials.2015.09.006

Weng QJ, Sun H, Fang CY, et al., 2021. Catalytic activity tunable ceria nanoparticles prevent chemotherapy-induced acute kidney injury without interference with chemotherapeutics. *Nat Commun*, 12:1436. https://doi.org/10.1038/s41467-021-21714-2

Wilson N, Kataura T, Korsgen ME, et al., 2023. The autophagy–NAD axis in longevity and disease. *Trends Cell Biol*, 33(9): 788-802. https://doi.org/10.1016/j.tcb.2023.02.004

Wu LK, Yang F, Xue YJ, et al., 2023. The biological functions of europium-containing biomaterials: a systematic review. *Mater Today Bio*, 19:100595. https://doi.org/10.1016/j.mtbio.2023.100595

Xie CL, Zhuang XX, Niu ZM, et al., 2022. Amelioration of Alzheimer's disease pathology by mitophagy inducers identified via machine learning and a cross-species workflow. *Nat Biomed Eng*, 6:76-93. https://doi.org/10.1038/s41551-021-00819-5

Xie YX, Jiang JN, Tang QY, et al., 2020. Iron oxide nanoparticles as autophagy intervention agents suppress hepatoma growth by enhancing tumoricidal autophagy. *Adv Sci*, 7(16):1903323. https://doi.org/10.1002/advs.201903323

Xu ST, Yang P, Qian K, et al., 2022. Modulating autophagic flux via ROS-responsive targeted micelles to restore neuronal proteostasis in Alzheimer's disease. *Bioact Mater*, 11:300-316. https://doi.org/10.1016/j.bioactmat.2021.09.017

Xue X, Wang LR, Sato Y, et al., 2014. Single-walled carbon nanotubes alleviate autophagic/lysosomal defects in primary glia from a mouse model of Alzheimer's disease. *Nano Lett*, 14(9):5110-5117. https://doi.org/10.1021/nl501839q

Yan S, Zheng X, Lin YQ, et al., 2023. Cas9-mediated replacement of expanded CAG repeats in a pig model of Huntington's disease. *Nat Biom Eng*, 7(5):629-646. https://doi.org/10.1038/s41551-023-01007-3

Yang L, Li P, Fu SN, et al., 2010. Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance. *Cell Metab*, 11(6):467-478. https://doi.org/10.1016/j.cmet.2010.04.005

Yang ZX, Ge CC, Liu JJ, et al., 2015. Destruction of amyloid fibrils by graphene through penetration and extraction of peptides. *Nanoscale*, 7(44):18725-18737. https://doi.org/10.1039/c5nr01172h

Yin Y, Tian BM, Li X, et al., 2022. Gold nanoparticles targeting the autophagy–lysosome system to combat the inflammation-compromised osteogenic potential of periodontal ligament stem cells: from mechanism to therapy. *Biomaterials*, 288:121743. https://doi.org/10.1016/j.biomaterials.2022.121743

Zeng JL, Martin A, Han X, et al., 2019a. Biodegradable PLGA nanoparticles restore lysosomal acidity and protect neural PC-12 cells against mitochondrial toxicity. *Ind Eng Chem Res*, 58(31):13910-13917. https://doi.org/10.1021/acs.iecr.9b02003

Zeng JL, Shirihai OS, Grinstaff MW, 2019b. Degradable nanoparticles restore lysosomal pH and autophagic flux in lipotoxic pancreatic beta cells. *Adv Healthcare Mater*, 8(12):1801511. https://doi.org/10.1002/adhm.201801511

Zeng JL, Acin-Perez R, Assali EA, et al., 2023. Restoration of lysosomal acidification rescues autophagy and metabolic dysfunction in non-alcoholic fatty liver disease. *Nat Commun*, 14:2573. https://doi.org/10.1038/s41467-023-38165-6

Zhang C, Ren J, He J, et al., 2018. Long-term monitoring of tumor-related autophagy *in vivo* by Fe_3O_4-NO· nanoparticles. *Biomaterials*, 179:186-198. https://doi.org/10.1016/j.biomaterials.2018.07.004

Zhang J, Qin X, Wang B, et al., 2017. Zinc oxide nanoparticles harness autophagy to induce cell death in lung epithelial cells. *Cell Death Dis*, 8(7):e2954. https://doi.org/10.1038/cddis.2017.337

Zhang JQ, Zhu SS, Jin PP, et al., 2020. Graphene oxide improves postoperative cognitive dysfunction by maximally alleviating amyloid beta burden in mice. *Theranostics*, 10(26):11908-11920. https://doi.org/10.7150/thno.50616

Zhang K, Zhu SO, Li JM, et al., 2021. Targeting autophagy using small-molecule compounds to improve potential therapy of Parkinson's disease. *Acta Pharm Sin B*, 11(10): 3015-3034. https://doi.org/10.1016/j.apsb.2021.02.016

Zhang W, Xu CC, Sun JC, et al., 2022. Impairment of the autophagy–lysosomal pathway in Alzheimer's diseases: pathogenic mechanisms and therapeutic potential. *Acta Pharm Sin B*, 12(3):1019-1040. https://doi.org/10.1016/j.apsb.2022.01.008

Zhang XW, Zhu XX, Tang DS, et al., 2023. Targeting autophagy in Alzheimer's disease: animal models and mechanisms. *Zool Res*, 44(6):1132-1145. https://doi.org/10.24272/j.issn.2095-8137.2023.294

Zhang XY, Misra SK, Moitra P, et al., 2023. Use of acidic nanoparticles to rescue macrophage lysosomal dysfunction in atherosclerosis. *Autophagy*, 19(3):886-903. https://doi.org/10.1080/15548627.2022.2108252

Zhang ZQ, Yue PF, Lu TQ, et al., 2021. Role of lysosomes in physiological activities, diseases, and therapy. *J Hematol Oncol*, 14:79. https://doi.org/10.1186/s13045-021-01087-1

Zhao JL, Tian ZM, Zhao SJ, et al., 2023. Insights into the effect of catalytic intratumoral lactate depletion on metabolic reprogramming and immune activation for antitumoral activity. *Adv Sci*, 10(4):2204808. https://doi.org/10.1002/advs.202204808

Zhao YG, Codogno P, Zhang H, 2021. Machinery, regulation and pathophysiological implications of autophagosome maturation. *Nat Rev Mol Cell Biol*, 22(11):733-750. https://doi.org/10.1038/s41580-021-00392-4

Zhou HL, Gong XQ, Lin HY, et al., 2018. Gold nanoparticles impair autophagy flux through shape-dependent endocytosis and lysosomal dysfunction. *J Mater Chem B*, 6(48):8127-8136. https://doi.org/10.1039/c8tb02390e

Zhu L, Wu GJ, Yang XY, et al., 2019. Low density lipoprotein mimics insulin action on autophagy and glucose uptake in endothelial cells. *Sci Rep*, 9:3020. https://doi.org/10.1038/s41598-019-39559-7

Zhu Q, Song JX, Chen JY, et al., 2023. Corynoxine B targets at HMGB1/2 to enhance autophagy for α-synuclein clearance in fly and rodent models of Parkinson's disease. *Acta Pharm Sin B*, 13(6):2701-2714. https://doi.org/10.1016/j.apsb.2023.03.011