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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 article, we introduce 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 regulating 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 article 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 nanoparticles; Transcription factor EB; Dementia; Alzheimer's disease

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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, 2023). The acidic environment within the lysosomal compartment is helpful for ensuring the optimal functioning of the 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, 2023).

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Autophagy, a highly conserved lysosome-dependent degradative procedure 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 they need to maintain the basic life activities of 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 causes the occurrence and progression of various diseases. Dysregulation of lysosomes and/or autophagy-lysosome systems is intimately 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). Hence, restoring the function of the lysosome and autophagy-lysosome system has become an increasingly important therapeutic strategy in disease management.

This article 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, together with the autophagic process. Second, various diseases associated with lysosomal/autophagic dysfunction are reviewed. Finally, we focus on engineered nanomaterials that have the ability to regulate the acidity and degradation capacity of lysosomes and restore 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.

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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, phosphatases, etc., 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., 2023). 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 mammalian target of rapamycin 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 protein 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 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-Phosphate 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 M6P 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 (ALP)

The autophagic process mediates the clearance of excess or aging cellular components, damaged proteins, lipids, nucleic acids, and 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 virtue of 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. What is more, LAMP-2A could specifically identify and bind to proteins carrying the 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 lies in the emergence of double membrane structural 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 cellular homeostasis(Martens and Fracchiolla, 2020).

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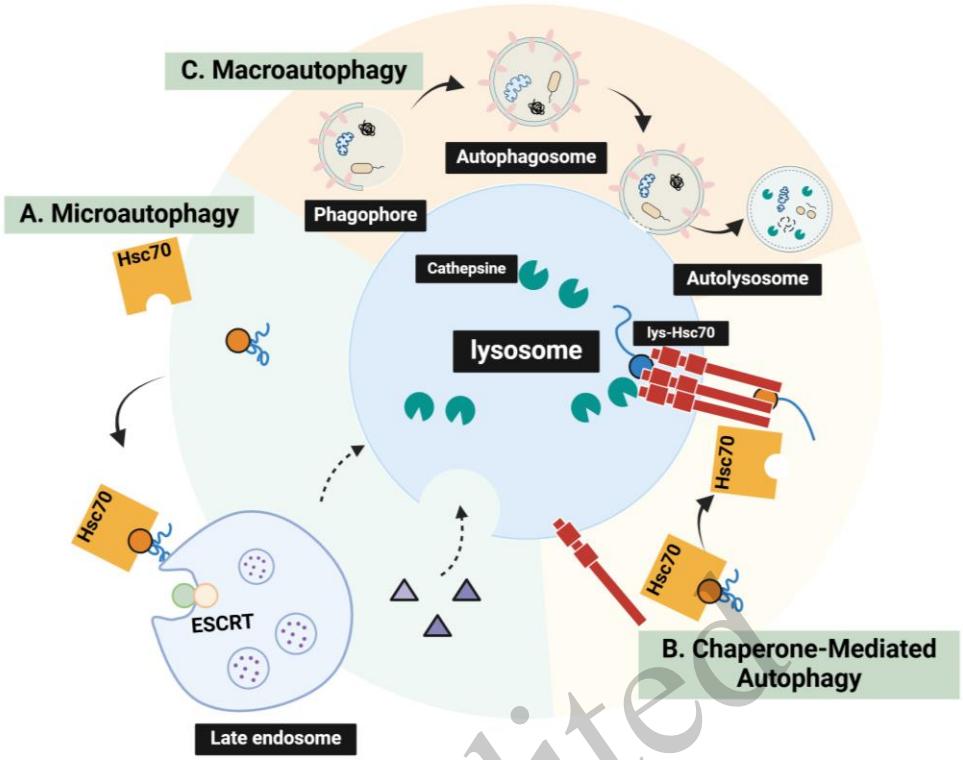

Fig. 1 Microautophagy (A), chaperone-mediated autophagy (B), and macroautophagy (C). Created by BioRender.com.

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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 development of neurodegenerative diseases, natural aging, inflammation-related diseases, non-alcoholic fatty liver disease (NAFLD), etc. (Aman, et al., 2021) (**Fig. 2**). Reasonable regulation and intervention of lysosome/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, such as mitochondria, is affected by lysosomal acidification dysfunction, which increases the production of reactive oxygen species (ROS) and inflammatory cytokines, leading to inflammatory diseases, cancer, and infectious diseases.

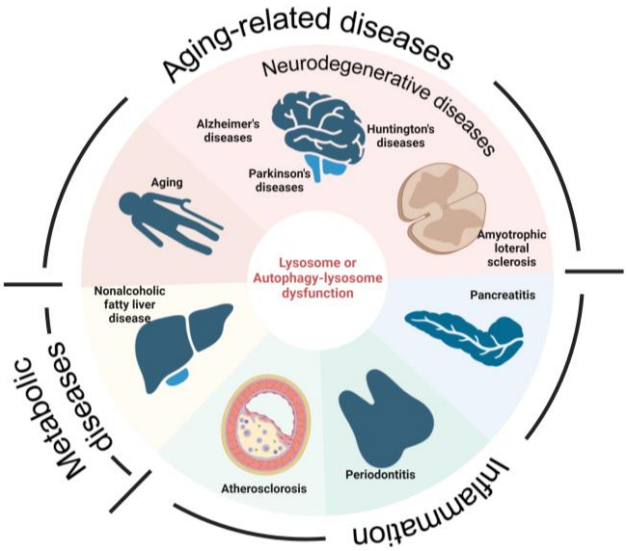

Fig. 2 Lysosomal/autophagic defects were closely related to various diseases. Created by BioRender.com.

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3.1 Neurodegenerative diseases

3.1.1 Alzheimer's disease (AD)

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 amyloid (Aβ) peptide and microtubule-associated protein tau (MAPT/tau) (Davoody et al., 2023), which can cause neuroinflammation and neuronal death (Zhang et al., 2022a). Therefore, a promising therapeutic strategy for AD is to eliminate Aβ and MAPT/tau aggregates (Lee and Nixon, 2022; Lee, et al., 2022; Xie et al., 2022; Iyaswamy et al., 2023; Zhang 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 mitophagy activity could contribute to the clearance of Aβ and tau and neuronal protection effects. Wang et al. (Wang et al., 2023) studied the interactions between pituitary adenylate-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. (Xu, et al., 2022) reported that the delivery efficiency of rapamycin to neurons in AD would be enhanced by ROS-responsive micelles, thereby improving autophagic flux and restoring neuronal proteostasis in AD. 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, 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 (PD)

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., 2020; Zhang et al., 2021a; Zhu et al., 2023).

3.1.3 Huntington's disease (HD)

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, 2017; 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 (Iyengar et al., 2023; Yan et al., 2023). The accumulation of the mHTT proteins in the central nervous system increases with ageing, 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 et al., 2021b). 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 (ALS)

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 the aggregated inclusions in both familial ALS patients and mouse models injected with the human SOD1 transgene containing a 93 glycine-to-alanine substitution (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. (Chen et al., 2011) experimentally validated that the dysregulation of autophagic

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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 NAFLD

NAFLD is a liver manifestation of metabolic syndrome, with lower levels of autophagy in liver cells (Lebeaupin et al., 2018). In patients with severe steatosis, autophagy substrate protein SQSTM1/p62 shows significant accumulation (Kashima et al., 2013; Fukuo 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 mammalian target of rapamycin (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 and the inactivation of Forkhead box O transcription factors (Frendo-Cumbo et al., 2021). Liver autophagy is similarly impaired in individuals with obesity, NAFLD, and insulin resistance (Ezquerro et al., 2018). 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 lysosome 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., 2019; He et al., 2021a).

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; Gukovskaya and Gukovsky, 2012; Mareninova et al., 2015). 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 autophagy-related 5 (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., 2017; Li et al., 2020a). 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), so PDLSCs are the most suitable for regenerating

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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. (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). Due 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, 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 ATG 13 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 exacerbates 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.

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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 (stroke, etc.), cancer, and neurodegenerative diseases. Aging-related diseases have become a significant globally 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 ATGs, LC3,

TFEB, SQSTM1/p62, etc.) 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 the cellular activity. NAD could be hydrolyzed by NAD +-consuming enzymes (NADases), finally downregulating 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 repairment of deoxyribonucleic acid (DNA) and the lifespan in various model systems (Fang et al., 2014; Fang et al., 2016; Presterud et al., 2023).

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 role 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, which is acidic and restores the lysosomal pH (**Fig. 3**).

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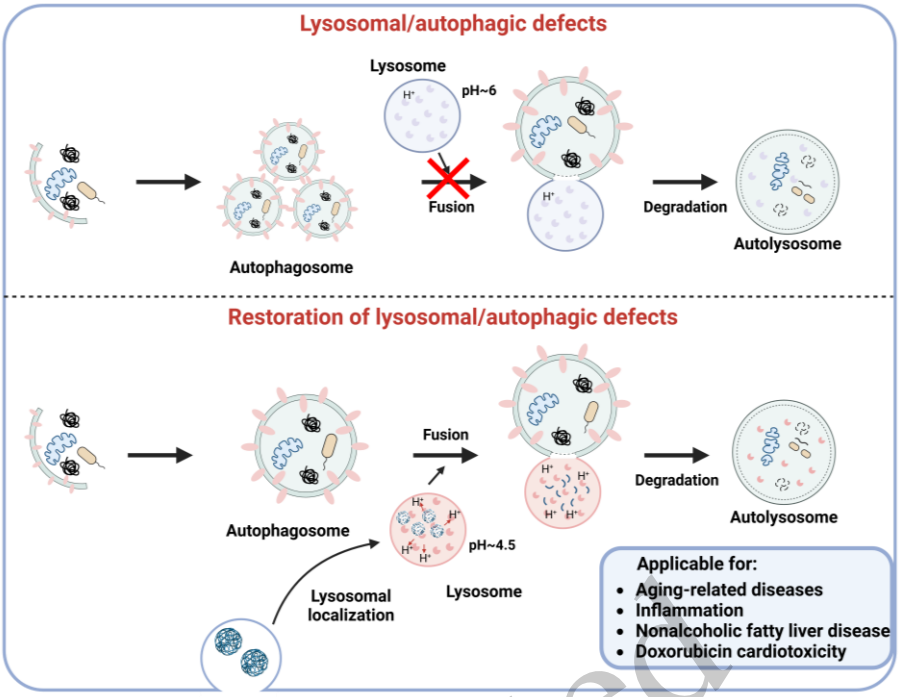

Fig. 3 Acidic nanoparticles, after internalization and location in lysosomes, would release acidic functional groups to acidify lysosomes, thereby restoring autophagy flux. Created by BioRender.com.

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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, 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 (Boulton et al., 2012). In this report, Gabriel, et al. revealed that acidic polymeric nanoparticles composed of PLGA 502H (PLGA ResomerH RG 502 H), PLGA 503H (PLGA ResomerH RG 502 H), or PLA (PLA ResomerH R 203S) could be localized in the lysosomes of human retinal pigment epithelial cells within 60 minutes, and nanoparticles composed of PLGA 503H 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 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. Benjamin et al. validated that acidic nanoparticles formed by PLGA could restore damaged lysosomal acidity and functionality in various pathological cell or disease models (Bourdenx et al., 2016). Their reports demonstrated that acidic nanoparticles prepared from PLGA (Resomer® RG 503H PLGA with a lactide:glycoside ratio of 50:50, molecular weight 24 000 to 38 000) could be transported to lysosomes within 24 hours 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, Benjamin et al. (Prévot et al., 2018) further developed an oil-in-water nanoemulsion loaded with PLGA (denoted as NE-PLGA). NE-PLGA exhibiting a high PLGA payload, meanwhile, 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, Grinstaff et al. (Zeng et al., 2019b) found that acidic nanoparticles formed by PLGA with a high glycolic acid (GA) to lactate (LA) ratio (GA:LA) were degraded faster in MPP^+-treated PC-12 cells, and exhibited stronger capabilities in terms of restoring lysosomal acidity and autophagic flux. Recently, Benjamin et al. (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 β-amyloid (Aβ) toxicity by restoring lysosomal membrane integrity, thus providing distinctive therapeutic possibilities in addressing AD. Kar and colleagues (Wang et al., 2020) found that the toxicity induced by $A\beta_{1-42}$ 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 damage 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; Koleini and Kardami, 2017; Li et al., 2018). Santin et al.(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**).

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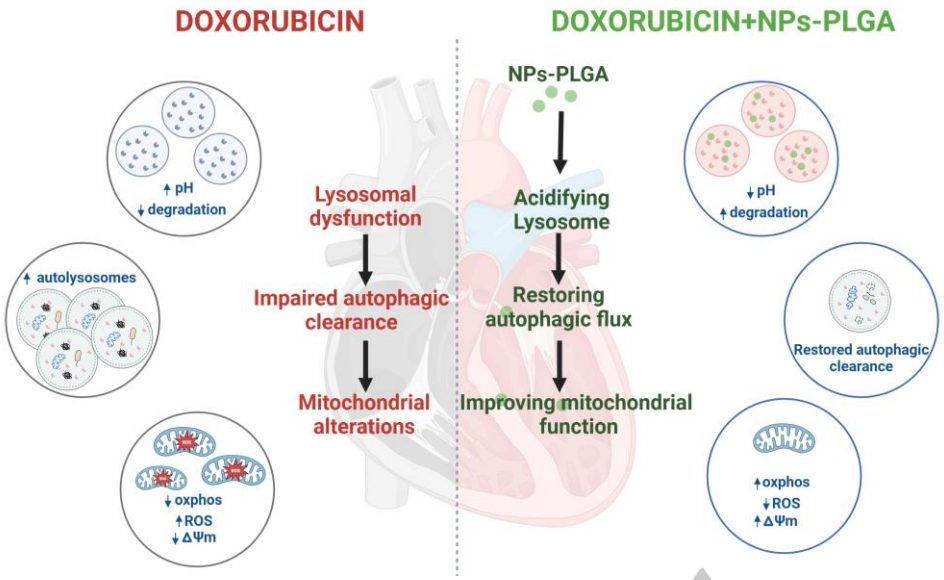

Fig. 4 Diagram of the inhalation of NPs-PLGA offering protection against Dox-induced cardiotoxicity by restoring lysosomal function. Created by BioRender.com according to Santin et al. (Santin, et al., 2023). OXPHOS, oxidative phosphorylation; ΔΨm, Mitochondrial membrane potential.

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PLGA-based core-shell acidic nanoparticles can also 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 monocytes and macrophages, potentially resulting in the degradation of cargo in lysosomes. Zhang, et al. (Zhang et al., 2022b) constructed core-shell acidic nanoparticles based on PLA and PLGA, respectively, and exploited them to target macrophage lysosomes, restoring their pH levels in conditions such as atherosclerosis. As illustrated, 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 showcased 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**).

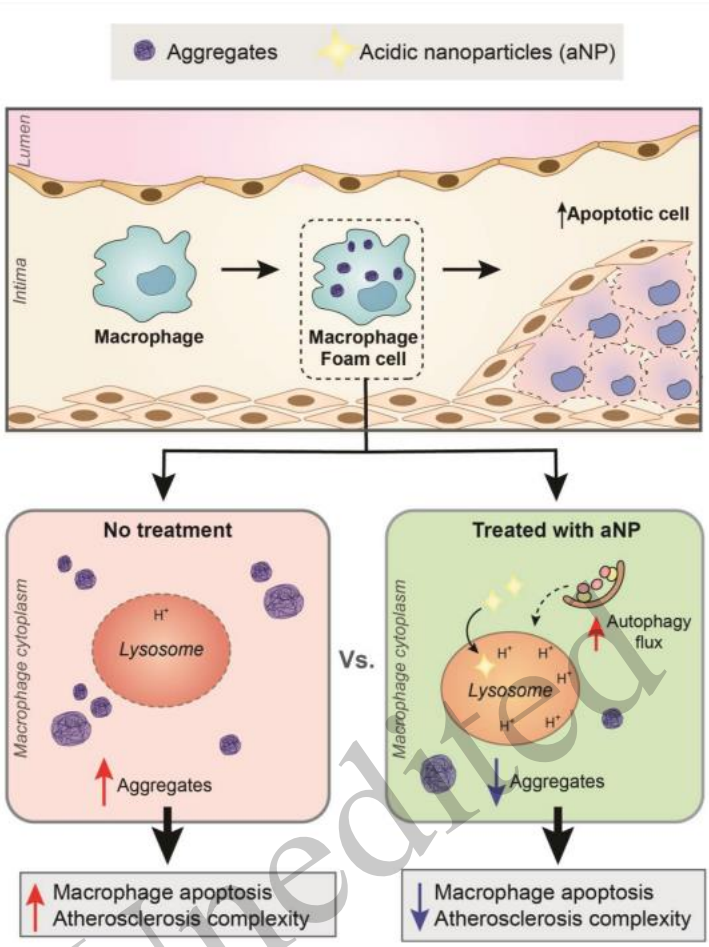

Fig. 5 Pattern diagram for rescuing macrophage lysosomal dysfunction using PLGA nanoparticles in atherosclerosis, created by BioRender.com according to Zhang et al. (Zhang, et al., 2022b).

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In pancreatic cells (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. Grinstaff and Shirihai et al. (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 acids exposure. Upon the addition of PLGA NPs, the extent of lysosomal pH restoration rises in proportion to the concentration of PLGA NPs, 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, PLGA NPs 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 autophagic degradation and clearance of accumulated autophagosomes. Treatment with PLGA NPs 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. In order

to ascertain whether lysosomal acidification damage is the cause of the inhibition of autophagy and cellular functions, Shirihai and Grinstaff et al. (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. Shirihai and Las et al. (Assali et al., 2018) 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, which can promote the recovery of lysosomal acidity under lipotoxicity and the acceleration of 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, Grinstaff and Shirihai et al. (Zeng, et al., 2023) showed that acid-activatable acidic nanoparticles (AcNPs) could target lysosomes and promote lysosomal re-acidification and autophagy flux. AcNPs, composing 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. AcNPs 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 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 AcNPs 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**).

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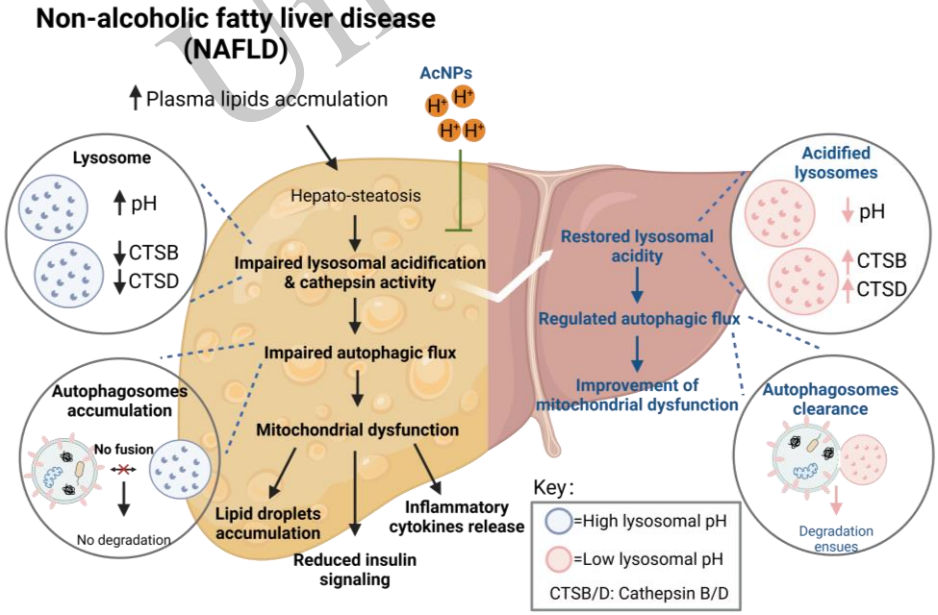

Fig. 6 The impact of impaired lysosomal function in NAFLD and the mechanism of action of AcNPs. Created by BioRender.com according to Zeng et al. (Zeng, et al., 2023).

4.1.3 Acidic Nucleolipids

Nucleolipids (NLs) 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). NLs can be either natural or synthetic. Regardless of their origin, in addition to their biological activities, such as their antibacterial, antifungal, or antitumor properties, they also have self-assembly capabilities (Van Tiel et al., 1985; Simeone et al., 2011; Riccardi et al., 2016). NLs are commonly considered as delivery carriers for active drugs, with documented capability to cross the blood-brain barrier (Swastika et al., 2019). Nanoemulsions (NEs) have certain advantages in delivering active drugs to the brain. Oil-in-water (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). Desvergnes et al. (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 closely resembling that of lactic acid and glycolic acid; the free acids help nucleolipids acidify quickly. Conversely, the second acid functional group protected in ester 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 themselves 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 (**Fig. 7B-C**). The encouraging results suggested that O/W NEs loaded with acidic NLs could function as efficient nano-carriers for active drugs. Since damage to an 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 NLs are readily transported to lysosomes and effectively recover the pH of impaired lysosomes.

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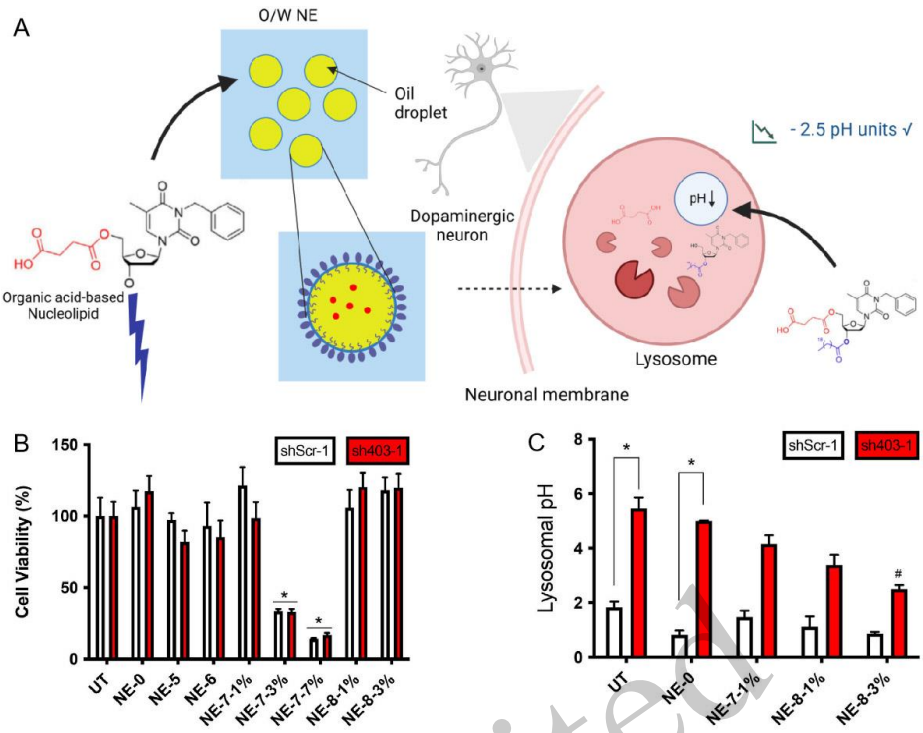

Fig. 7. Nucleolipidic nanoemulsions for neuronal lysosomal acidification. (A) Illustration of acidification of neuronal lysosomal using nucleolipidic nanoemulsions, which was redrawn with BioRender.com according to Brouillard et al. (Brouillard, et al., 2021). (B) Cell viability in control and ATP13A2-depleted M17 cells. (C) Acidic NEs restore lysosomal pH in vitro. Reproduced from Brouillard et al. (Brouillard, et al., 2021) licensed under Creative Commons CC BY 4.0.

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Brouillard et al. (Brouillard et al., 2023) synthesized a DNA-derived nanocarrier, in which the NLs are covalently linked to lipids with biocompatible organic acids as active components. They could be effectively integrated into O/W NEs carriers and 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 NLs post cellular uptake and their ability to completely restore lysosomal acidity at 40 μM. From a pharmaceutical perspective, to enhance the stability and reduce overall concentration of NL-based prodrugs, nucleolipid oligomerization emerged as an interesting chemical modification (Brouillard, et al., 2021). Subsequently, Desvergnes et al. 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 NL-based nanosystems and underscore lysosomal restoration as a promising strategy for the treatment of PD and other age-related protein diseases.

Table 1 Acidic nanoparticles capable of restoring lysosomal or autophagic function

Biomaterial Types	Size; Zeta Potential	Composition	Diseases	Models	Biological Effect	Ref.
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 503H; PLA	Macular degeneration	ARPE-19 cells	Restoring lysosomal functions	(Boulton, 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	Resomer® RG 503H PLGA	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 and 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 nm; +8 mV	silica nanoparticles; PLGA Resomer™-RG502 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-polyacrycl ic acid	Atherosclerosis	C57BL/6 J strain or apoe−/− mice on C57BL/ 6 J background	Rescuing macrophage lysosomal dysfunction	(Zhang, et al., 2022b)
PLGA nanoparticles	~100 nm, -27 mV	Resomer® RG 503H PLGA, lactic acid/glycolic acid 50:50	Type II diabetes	INS1 cells	Lowering lysosomal pH, restoring autophagic flux	(Zeng, et al., 2019b)
Photoactivatable, acidic NPs (paNPs)	~100 nm	2-nitrobenzaldehyde, succinic acid O,O'-(2-((methacryloyloxy)methyl)-2-methylpropane-1,3-diyl) bis(1-(2-nitrophenyl)ethyl) disuccinate, 1,4-O-methacrylo	diabetes	INS1 832/13 cells, C57Bl6 male mice islet cells	Enhancing lysosomal acidity and function, restoring autophagy, improving insulin secretion	(Trudeau, et al., 2016)

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		ylhydroquinone				
paNPs	~100 nm	2-nitrobenzaldehyde, succinic acid;	Genetic disorders, neurodegenerative diseases, obesity, type 2 diabetes	INS1 cells, C57BL/6J male mice islets	Restoring of lysosomal acidity; recovering mitochondrial turnover and function	(Assali, et al., 2018)
Acid-activated acidic nanoparticles	~100 nm; -25 ~ -30 mV	tetrafluorosuccinic 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; -25~ -35 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; -30~-40 mV	Succinic acid, nucleoside, lipid	PD	BE(2)-M17 cells	Recovering lysosomal pH	(Brouillard, et al., 2023)

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4.2 Inorganic non-metallic nanoparticles

Several kinds of inorganic non-metallic nanoparticles, including graphene oxide, nano-selenium, carbon nanotubes, and graphene quantum dots, 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 (GO)

Xu et al. (Liu et al., 2016) explored the impact of GO on polychlorinated biphenyls (PCBs)-induced cytotoxicity. They demonstrated that pre-treatment with GO could reduce the cytotoxicity induced by 2, 2, 5-tetrachlorobiphenyl (PCB52, an ortho-substituted non-planar homolog) and mutations in the 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 studies 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. The abnormal accumulation of prion proteins with protease-resistant misfolded conformations is the pathological mechanism of prion diseases. Park et al. (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 et al., 2023b). Studies have also shown that enhancing autophagic flux can significantly promote the degradation of Aβ protein and effectively alleviate cytotoxicity. Yang et al. (Li et al., 2020b) 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 5'-monophosphate (AMP)-activated protein kinase (AMPK)-mTOR signaling pathway. Yang et al. further validated the neuroprotective effect of GO using a mouse model of AD (Chu et al., 2020).

Zhang et al. (Zhang et al., 2020) further elaborated that GO could inhibit β-cleavage of amyloid precursor proteins and promote the delivery of intracellular Aβ 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 et al., 2021b). Nano selenium has been reported to restore impaired cellular autophagic flux. Cadmium (Cd) 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. (Hu et al., 2022) selected mouse testicular interstitial cells (TM3) 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 electrochemical active surface area, effective thermal conductivity, superior electron conductivity, and exceptional mechanical strength, making them suitable for various applications in nanomedicine, such as in stroke, neurological disorders, schizophrenia, etc.(Kyle and Saha, 2014). Xue et al. (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-level phosphorylation status of mTOR in SWNT-treated 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. This functionalized SWNTs can reverse the aberrant activation of mTOR signal and repair lysosomal proteolysis defects, thereby restoring autophagy and promoting the clearance of autophagic substrates.

4.2.4 Graphene quantum dots (GQDs)

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 (Sheikh Mohd Ghazali et al., 2023). Kim et al. (Kim et al., 2018) found that GQDs could inhibit the fibrillization of mutant α-syn, thereby protecting neurons in PD. Kang et al. (Kang et al., 2021) evaluated the potential of GQDs to treat the Niemann–Pick disease type C in a transmembrane protein (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.

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

Biomaterial Types	Characterizations	Diseases	Models	Mechanism of action	Concentrations	Biological Effect	Ref.
GO	Single layer; Large GO: 2.4 μm (hydrodynamic size), -11.9 ± 1.75	HD	HeLa, PC12 cells	Enhancing autophagic flux and ubiquitination of huntingtin protein	60 μg/mL	Enhancing the clearance of mutant huntingtin	(Jin, et al., 2016)

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	mV; Small GO: 200 nm (hydrodynamic size), -30.0 ± 2.06 mV						
GO	Mostly less than 1 μm; average thickness was approximately 1 nm	Prion diseases	human neuroblastoma cell line SK-N-SH	Restore autophagic flux impaired by prion protein peptides	8 mg/L	Preventing prion-mediated mitochondrial neurotoxicity	(Jeong, et al., 2017)
GO	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, et al., 2020b)
GO	Single-layer nanosheet shape; ~ 200 nm (hydrodynamic size); -30.0 ± 2.06 mV	postoperative cognitive dysfunction	HKE293T cells, SHSY5Y cells, female C57BL/6 mices	Reducing Aβ generation, enhancing lysosome mediated Aβ degradation	60 μg/mL	Improving cognitive function of the postoperative mice	(Zhang, et al., 2020)
GO	0.945 nm (average thickness); 253.10 ± 10.78 nm (hydrodynamic size); -46.00 ± 1.08 mV (charge)	Polychlorinated biphenyls (PCBs)-induced toxicity	The 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	~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., 2022)
SWNTs	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)
GQDs	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 patient, 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, and protecting the loss of Purkinje cells in the cerebellum	(Kang, et al., 2021)

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4.3 Metal-based nanoparticles

Gold nanoparticles, cerium oxide nanoparticles, zinc oxide 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**).

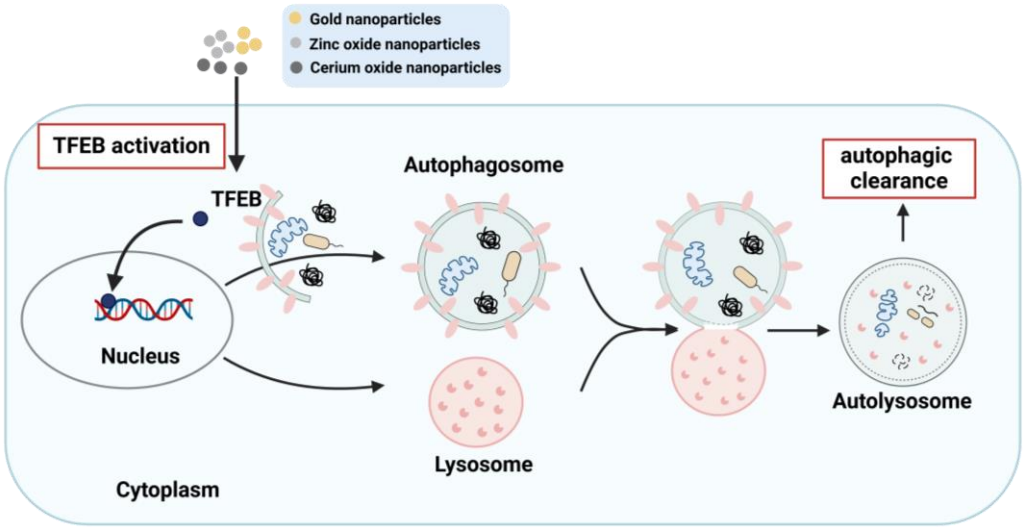

Fig. 8 Graphical illustration of the main regulatory mechanism of several metal-based nanomaterials in modulating lysosomal activity and autophagy-lysosome pathway activity. Created by BioRender.com.

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4.3.1 Gold nanoparticles (AuNPs)

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., 2017), the intracellular uptake and subsequent lysosomal retention of AuNPs (Huang et al., 2023) provide an important clue for targeting interventions for lysosome-related diseases. Stochaj et al. (Maysinger et al., 2020) found that gold nanoclusters surface-modified with glutathione or polyethylene glycol (PEG), even at sub-lethal concentrations, still could 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, suggesting the capability of gold nanoparticles to regulate lysosomal biology. Recently, Chen et al. (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-nanometer-sized AuNPs, indicated by the restoration of lysosomal size plus acidity and the enhancing 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 expressions and subsequently restore lysosomal degradation ability, exhibiting a certain recovery effect on the osteogenic possibility of I-PDLSCs (**Fig. 9**).

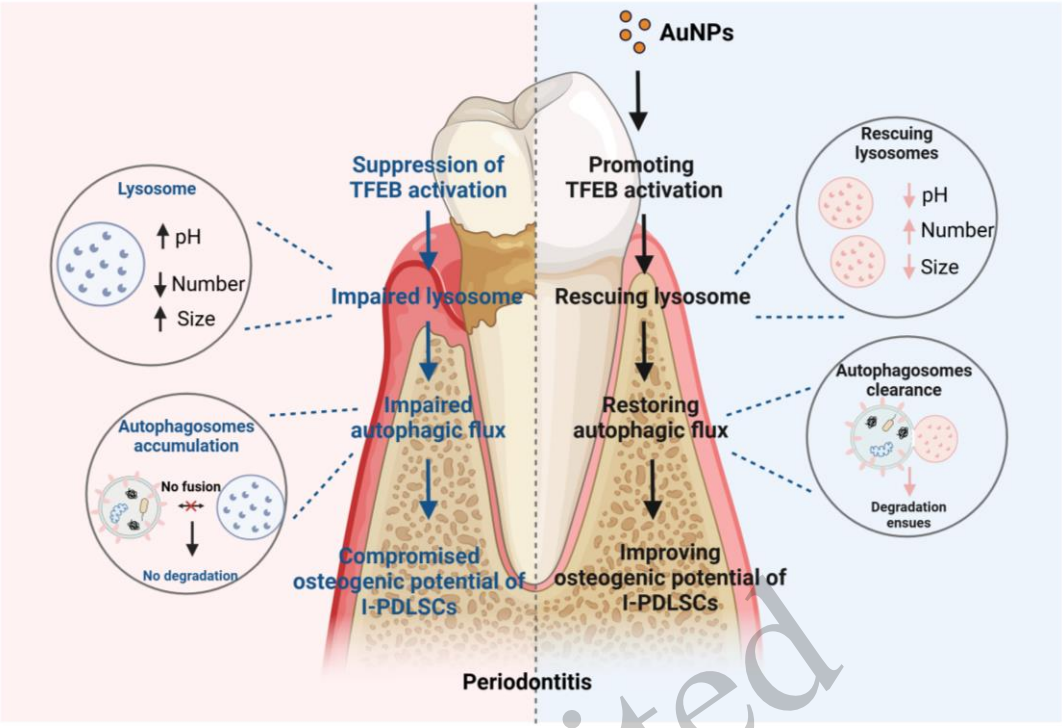

Fig. 9 Graphical illustration for restoring autophagy and osteogenic potential of I-PDLSCs by AuNPs. AuNPs could activate TFEB, restore lysosomal size and acidity, rescue autophagosome-lysosomal fusion, and improve autophagic activity and osteogenic potential in I-PDLSCs. Created with BioRender.com.

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4.3.2 Cerium oxide nanoparticles (nanoceria)

Nanoceria possesses various biological effects, including antioxidant, anti-tumor, antibacterial, and neuroprotective properties (Kim et al., 2023b), and has been utilized in the treatment of arthritis (Chen et al., 2023a), tumors (Zhao et al., 2022), stroke (He et al., 2020), chemotherapy-induced kidney damage (Weng et al., 2021), and other diseases. Nanoceria possesses free radical scavenger 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. Yoon et al. (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 and 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 acute kidney injury by protecting kidney structure and glomerular function.

Nanoceria has 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. Maccarone et al. (Tisi et al., 2020) found that nanoceria protected ARPE-19 cells against H_2O_2-induced cell damage. Maccarone et al. (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 prior to light damage prevented RPE cell death and degeneration. They found that cerium dioxide nanoparticles were localized in the 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 Fe-based metal oxides

Iron-based nanoparticles hold potential applications in various biomedical fields, such as magnetic navigation, drug delivery, bioimaging, etc. Specifically, iron oxide nanoparticles such as Ferumoxytol have received U.S. Food and Drug Administration 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. Shi et al. (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. Chen et al. (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 activity, restoring autophagy flux, and alleviating tubular damage.

4.3.4 ZnO nanoparticles

After cellular internalization of zinc oxide 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., 2023a). Zinc oxide nanoparticles, exhibiting selective toxicity against tumor cells, have also been studied as a potential therapeutic agent for cancer. In addition to the transformation of zinc oxide nanoparticles upon internalization into lysosome-related organelles, the nanoparticles themselves could also modulate lysosome-related molecular events. Popp and Segatori (Popp and Segatori, 2019) assessed the impact of zinc oxide 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, Li et al. (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 mitigated the pyroptosis induced by ZnO nanoparticles in liver cells. Collectively, the surface modification and size of zinc oxide nanoparticles may affect their regulation of the lysosome/ALP, which provides an important insight for the future design of nano- and micro-sized zinc oxide materials with expected lysosomal or autophagic regulatory properties.

4.3.5 Europium hydroxide nanorods

Materials containing the rare earth element europium exhibit 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. (Wei et al., 2014; Wei et al., 2015) illustrated that europium hydroxide nanorods could clear mutant huntingtin proteins expressed in Neuro 2a or PC12 cells by inducing protein kinase B (AKT)-mTOR and AMPK independent autophagy. Functionally sound lysosomes or 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 lysosome. Furthermore, these 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.

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

Biomaterial Types	Characterizations	Diseases	Models	Concentrations	Biological Effect	Ref.
Gold nanoclusters	Surface-modified with glutathione or polyethylene glycol (PEG); ~3 nm	Glioblastoma	Human glioblastoma U251N cells	⩽1 μM	Regulating lysosome biology, causing hemostatic perturbations	(Maysinger, et al., 2020)
AuNPs	40 nm	Periodontitis	PDLSCs	0.01 nM	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% g/ml	Promoting the activation of TFEB and inducing the upregulation of ALP related genes	(Song et al., 2014)
Nanoceria	$Ce(NO_3)_3 \cdot 6H_2O$;ethylene glycol; NH_4OH	Age-related macular degeneration	ARPE-19 cells	1 nM	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 ± 6.79 nm; 20.3 ± 1.6 mV	Salmonella infection	chicken	50 mg/kg	Regulating ROS, phosphorylation of mTOR, 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 MMP-2 activity and restoring autophagy flux	(Liu, et al., 2021)
Zinc oxide 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 over-expressing HeLa cells	20 μg/mL	Activating TFEB regulated ALP and the clearance of lipofuscin	(Popp and Segatori, 2019)
Europium hydroxide nanorods	a length 80~160 nm and a diameter 25~40 nm	HD	EGFP-Htt(Q74) overexpression Neuro2a or PC12 cells; Hela cells	50 μg/mL	Enhancing lysosome acidity, maturation of cathepsin D and clearing huntingtin protein aggregation	(Wei, et al., 2014; Wei, et al., 2015)

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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, atherosclerosis, etc.—closely related to lysosomal/autophagic lysosomal 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 have the capability to 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 nanoemulsions. Acidic nanomaterials usually contain stimuli-responsive and biodegradable covalent linkages, and upon effective degradation in lysosomes, could release the acidic functional group and restore lysosomal pH. Inorganic nanoparticles, including gold nanoparticles, cerium oxide nanoparticles, zinc oxide nanoparticles, and others, have been reported to enhance the activity of the lysosome 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 bafamycin A1 and the lysosomal protease inhibitor 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 purposes. 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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Data availability statement

Please refer to the detailed information in the following websites (https://www.springer.com/us/editorial-policies/data-availability-statement; https://www.springernature.com/gp/authors/research-data-policy/data-availability-statements)

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Author contributions

Xiaodan HUANG, Yue FANG and Jie SONG were involved in investigation, writing–original draft, and visualization.

Yuanjing HAO and Yuanyuan CAI were involved in investigation, writing–original draft, and visualization. Pengfei WEI and Na ZHANG were involved in 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 there is no conflict of interest between them. This review does not include any research conducted by the author on human or animal subjects.

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