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Lysosomes: guardians and healers within cells- multifaceted perspective and outlook from injury repair to disease treatment

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Abstract

Lysosomes, as crucial organelles within cells, carry out diverse biological functions such as waste degradation, regulation of the cellular environment, and precise control of cell signaling. This paper reviews the core functions and structural characteristics of lysosomes, and delves into the current research status of lysosomes damage repair mechanisms. Subsequently, we explore in depth the close association between lysosomes and various diseases, including but not limited to age-related chronic diseases, neuro-degenerative diseases, tumors, inflammation, and immune imbalance. Additionally, we also provide a detailed discussion of the application of lysosome-targeted substances in the field of regenerative medicine, especially the enormous potential demonstrated in key areas such as stem cell regulation and therapy, and myocardial cell repair. Though the integration of multidisciplinary research efforts, we believe that lysosomes damage repair mechanisms will demonstrate even greater application value in disease treatment and regenerative medicine.

Overview of lysosomes structure and function

Since Belgian scientist Cristian de Duve first revealed the existence of lysosomes in 1955, the complex functions and structural characteristics of this organelle have gradually become a hot topic in biological research. In 2005, de Duve further defined lysosomes as the central hub for degradation and metabolism in cells, emphasizing their core role in maintaining cellular homeostasis [1]. Lysosomes, organelles with a single-membrane structure, are widely present in eukaryotic cells, exhibiting diverse morphologies, often spherical or elliptical, with diameters ranging from 0.2 to 0.8 micrometers [2]. The lysosomal membrane structure consists of a bilayer of phospholipids and is rich in high-carbohydrate compounds, imparting the lysosomal membrane with high stability and selective permeability [3, 4]. This not only helps maintain the acidic environment within lysosomes but also protects the hydrolytic enzymes inside from

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interference by other cellular components, ensuring a stable and efficient microenvironment [5].

The key components of the lysosomal membrane are glycosylated membrane proteins, which not only contribute to maintaining the structural integrity of lysosomes but also are responsible for executing various biological functions [6]. They possess specific transmembrane structures that firmly anchor them to the membrane, and their specific functional domains enable them to interact intricately with other molecules, participating in complex processes such as substance transport and signal transduction within lysosomes. Several types of membrane proteins in lysosomes are particularly crucial. Firstly, carrier proteins, which can specifically bind and transport specific substances such as amino acids and glucose. Through subtle conformational changes, achieve the transmembrane transport of substances, thus meeting the cell's requirements for nutrient intake and metabolism [7]. Secondly, channel proteins, which form channels on the lysosomal membrane, allowing specific substances, such as hydrogen ions, to diffuse across the membrane along concentration gradients. For example, the proton pump V-ATPase, as an important channel protein, plays a crucial role in maintaining the acidic environment within lysosomes. In addition, there are receptor proteins on the lysosomal membrane that can recognize and bind specific molecules, such as extracellular matrix components and pathogens. These receptor proteins play important roles in signal transduction processes, regulating cellular proliferation, differentiation, apoptosis, and other life activities [8]. Enzyme proteins are also indispensable components on the lysosomal membrane, they can catalyze specific chemical reactions, such as phosphorylation and dephosphorylation, which play a crucial role in signal transduction pathways, affecting intracellular signal transduction. The highly acidic environment inside lysosomes is key to their digestive function. The maintenance of this environment is attributed to the stable properties of the lysosomal membrane and the efficient operation of proton pumps on the membrane [9]. These proton pumps, acting as transmembrane protein complexes, continuously transport hydrogen ions from the cytosol into the lysosome, thereby precisely regulating its internal pH to approximately 5.0. The central structure of the proton pump is the V-type ATPase (Vacuolar H ± ATPase, V-ATPase), which is elegantly composed of a catalytic core on the cytosolic side and a proton channel on the lysosome membrane. The catalytic core is responsible for hydrolyzing ATP to provide energy, while the proton channel ensures the smooth entry of hydrogen ions into the interior of the lysosome [10]. This unique design allows the lysosome to maintain its acidic internal environment while consuming ATP.

Lysosomes contain approximately 60 types of hydrolytic enzymes, including proteases, nucleases, glycosidases, lipases, and phosphatases, which exist in high concentrations within lysosomes and possess efficient catalytic functions [11]. These hydrolases are able to recognize and break down various biological macromolecules, such as proteins, polysaccharides, nucleic acids, and lipids, with high specificity and efficiency in their degradation processes [12]. By precisely regulating the activity of these hydrolases, the lysosome is able to rapidly and accurately degrade phagocytosed materials, thereby providing the cell with essential nutrients and energy. This function renders the lysosome an indispensable role in cellular metabolism and homeostasis maintenance, earning it the informal name of the cell's 'digestive workshop'.

However, the functions of the lysosome extend far beyond these. It is not merely a digestive factory, but also plays a crucial role in numerous physiological processes within the cell [13]. Current research suggests that the lysosome is a crucial organelle involved in innate and adaptive immunity, as well as nutrient sensing [14]. Abnormalities in lysosome function are closely related to the occurrence and development of many diseases [15] (Fig. 1), we will explore the association between lysosome damage, repair mechanisms, and diseases, particularly in the context of aging, neurodegenerative diseases, tumor development, regenerative medicine, inflammation, and immune regulation.

The repair of lysosome damage

The connection between lysosomal damage and cell death pathways

Lysosomes, as critical organelles within cells, play important roles in maintaining cellular metabolism and waste degradation. However, when lysosomes are damaged, such as membrane rupture or impairment, their internal enzymes and acidic substances can leak into the cytoplasm, disrupting the intracellular environment and causing cell damage [16, 17]. Various factors, such as oxidative stress, drug effects, and viral infections, can trigger lysosomal damage. Lysosomal damage is a key step in the occurrence and development of many diseases. It is worth noting that lysosomal damage is closely related to various cell death pathways. Specifically, damaged lysosomes can trigger the mitochondrial pathway, leading to the release of cytochrome C from mitochondria, activate the caspase family, and ultimately trigger cell apoptosis. Additionally, the tissue proteases released from lysosomal damage also play a crucial role in cell necrosis and pyroptosis processes. They can cleave caspase-8, activate the RIPK (Receptor-interacting serine/threonine-protein kinase) pathway, leading to necroptosis of cells, and simultaneously activate inflammasomes and caspase-1,

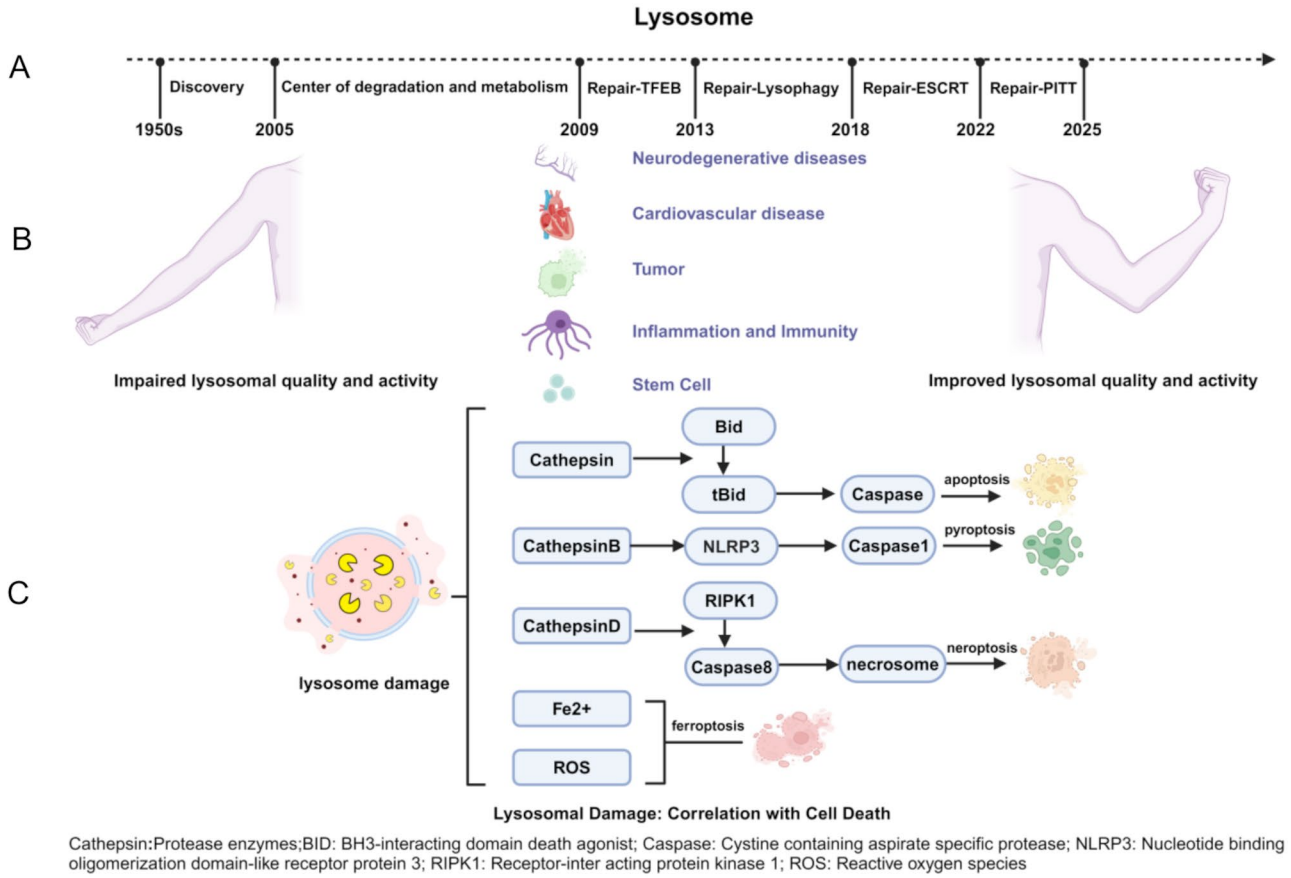


Fig. 1 Lysosome: A Journey of Discovery and its Role in Cell Fate. **A**: The timeline depicts the historical discovery of the lysosome's role in cellular processes. **B**: Impaired lysosomal quality and activity is linked to a range of diseases. **C**: Lysosomal dysfunction can lead to various forms of programmed cell death including apoptosis, pyroptosis, and necroptosis. These pathways involve the activation of caspases and other molecules

inducing cell pyroptosis [18, 19]. Moreover, studies have shown that the reactive oxygen species and iron released from lysosomal damage are important promoting factors for ferroptosis. Additionally, lysosomal damage can activate pro-apoptotic proteins like Bax, directly inducing cell apoptosis, while extensive lysosomal damage may lead directly to cell necrosis [20, 21]. Lysosomal damage is closely related to various cell death pathways, and the extent of damage plays a crucial role in determining the choice of cell death pathways [22]. Therefore, the study of lysosomal damage and repair mechanisms is of significant theoretical and clinical importance.

Characteristics of lysosomal damage - progress in lysosomal membrane permeabilization (LMP) mechanism

Lysosomes, as the hub for intracellular degradation of macromolecules, once their membrane permeability is compromised, can experience leakage of their internal components such as tissue proteases into the cytoplasm, thereby triggering lysosome-dependent cell death. This phenomenon of membrane permeabilization, known as LMP, is often triggered by various cellular stress factors and becomes a crucial link in the cell death pathway.

Regulated cell death (RCD) mechanisms depend on the activation and recruitment of specific pore-forming proteins (PFP), which act as executors of various cell death pathways. In the process of apoptosis, regulatory factors such as BAX, BAK, and BOK play crucial roles; while in the processes of pyroptosis and necroptosis, gasdermins (GSDM) and mixed-lineage kinase domain-like protein (MLKL) play important roles. The inactive precursors of these PFPs are transformed into pore-forming entities through a series of complex processes - including activation, membrane targeting, membrane insertion, and oligomerization-becoming the driving factor of LMP in cell death pathways [23]. New research has confirmed that during the initiation of necroptosis, MLKL is activated and translocated to the lysosomal membrane. Subsequently, the oligomerization of MLKL induces lysosomal aggregation and fusion, ultimately triggering LMP. This permeabilization process leads to the rapid release of lysosomal contents into the cytoplasm, thereby causing a sharp increase in levels of cathepsins, including cathepsin

B (CTSB), which becomes a key factor in necroptosis due to its ability to degrade many essential proteins for cell survival. Additionally, the N-terminal domain (NTD) of MLKL can also trigger LMP during the induction of oligomerization, leading to the release of CTSB and subsequent cell death. These findings not only reveal that MLKL-induced lysosomal membrane permeabilization (MPI-LMP) plays a crucial role in necroptosis, but also shed light on the mechanisms by which pore-forming proteins contribute to regulated cell death pathways [23].

Sicca syndrome(SS), a chronic progressive autoimmune disease, is primarily characterized by xerostomia, xerophthalmia, and the presence of specific autoantibodies. Researchers have discovered that an increase in LAMP3 expression leads to the degradation of LAMP1, thereby promoting LMP and the relocalization of cathepsins to the cytoplasm. These changes not only induce instability in autophagic flux but also activate caspases, accelerating the process of apoptosis [24, 25]. In studies of hepatocellular lipotoxic injury, it has been found that the apoptotic protein BAX can recruit the necroptotic executor protein MLKL to lysosomes, revealing the crucial role of lipotoxicity as a trigger for LMP in hepatocytes across various ALD (Adrenoleukodystrophy) models. Concurrent inhibition of BAX or MLKL through pharmacological or genetic means can effectively protect hepatocytes from LMP damage induced by lipotoxicity. This discovery not only deepens our understanding of the LMP mechanism in hepatocytes but also provides new insights and methods for the prevention and treatment of related diseases [26]. Similarly, in clear cell renal cell carcinoma (ccRCC), serine hydroxymethyltransferase 2 (SHMT2) affects the LMP process through metabolic reprogramming, promoting the progression of ccRCC. The specific mechanism involves SHMT2 depletion interfering with one-carbon metabolism, increasing reactive oxygen species levels, decreasing ATP, disrupting cellular homeostasis, and activating autophagy. Fusion of autophagosomes with lysosomes leads to LMP, ultimately inducing apoptosis [27].

Ursolic acid, a natural pentacyclic triterpenoid compound, exhibits significant anticancer activity in the treatment of breast cancer. Experimental studies have revealed that ursolic acid can affect lysosomal function in breast cancer cells, increasing lysosomal pH, altering cellular lipid distribution, and subsequently inducing LMP and lysosomal enzyme leakage. This process precedes apoptosis, suggesting that it is an initial event in ursolic acid-induced cell death. In addition, the combined use of ursolic acid with cationic amphiphilic drugs can significantly enhance LMP and the degree of cell death. Thus, ursolic acid plays a crucial role in breast cancer treatment by affecting lysosomal function [28]. Notably, P53 exhibits complex interactions with lysosomes during the cellular response to DNA damage. On one hand, P53 induces LMP by upregulating and activating BID, which subsequently triggers cell death, on the other hand, P53 activates autophagy through the mTOR pathway to eliminate damaged lysosomes, serving as a self-protection mechanism for the cell [29].

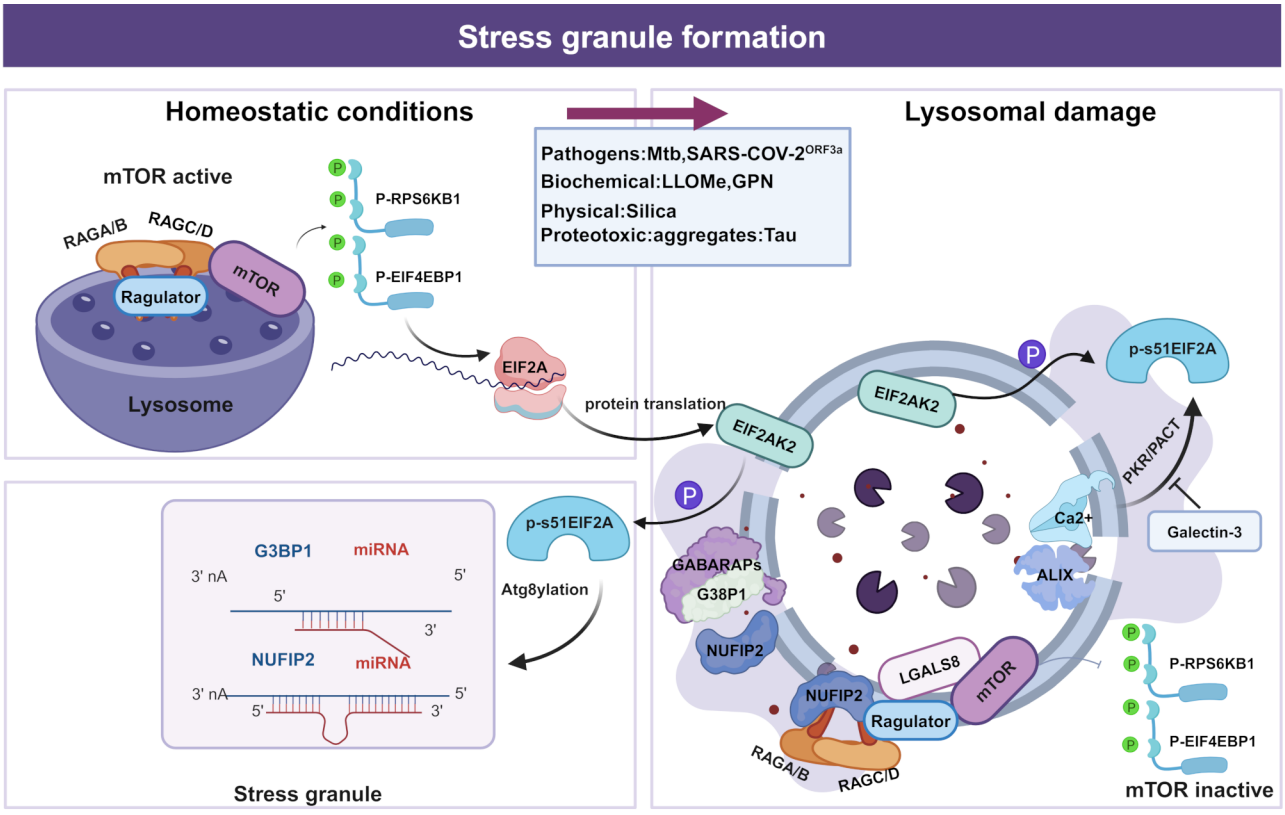
In summary, lysosomal membrane permeabilization serves as a critical step in cell death, and it is finely regulated by multiple factors. Through in-depth investigation of these regulatory mechanisms, we hope to provide new strategies and targets for the treatment of related diseases.

Lysosomal damage and stress granule (SG) formation

Stress granules are biomolecular condensates in the cytosol composed of proteins and RNA that assemble into 0.1–2 μm membraneless organelles when the cell is under stress.Environmental stressors trigger cellular signaling, eventually leading to the formation of stress granules.Stress granule formation is often downstream of the stress-activated phosphorylation of eukaryotic translation initiation factor eIF2α; this does not hold true for all types of stressors that induce stress granules [30], for instance, eIF4A inhibition.Besides, Recent research demonstrates that lysosomal damage can induce the formation of SG [31]. Various lysosomal damaging agents, including SARS-CoV-2 ORF3a (Open reading frame 3a), mycobacterium tuberculosis, and proteopathic tau, can induce the formation of SGs. During lysosomal damage, mammalian ATG8s interact directly with core SG proteins NUFIP2 and G3BP1. This ATG8 modification is crucial for recruiting them independently of SG condensates to damaged lysosomes. Subsequently, NUFIP2 promotes mTOR inactivation through the Ragulator-RagA/B complex [32, 33]. This process involves membrane ATG8 (Autophagy-related protein 8) modification, coordinating the formation of SGs during lysosomal stress and mTOR inactivation. In 2024, the research unit demonstrated that the formation of SGs is initiated through a calcium-dependent pathway, which paradoxically promotes cell survival after lysosomal damage. Mechanistically, the ALIX protein can sense calcium leakage and induce SG formation by regulating the phosphorylation of eIF2α. In this process, ALIX plays a crucial role by modulating the interaction between PKR and its activator PACT, while galectin-3 exerts a negative impact on this process. It is worth noting that these regulatory events all occur on damaged lysosomes. This study not only reveals a novel mechanism by which lysosomal damage triggers SG formation but also provides insight into the interaction between lysosomes and SGs (Fig. 2). Importantly, SG formation plays a significant role in promoting cell survival in various physiological contexts, such as SARS-CoV-2 infection and adenovirus infection [34, 35].

Progress in lysosomal damage repair mechanisms

In recent years, scientists have conducted in-depth research on the mechanisms of lysosomal damage repair, revealing processes such as lysosomal restoration, lysosomal autophagy, and lysosomal regeneration. These processes coordinate with each other to maintain the normal function of lysosomes. Lysosomal repair involves protein restoration and membrane regeneration to restore the normal function of damaged lysosomes. Lysosomal autophagy degrades damaged lysosomes or their contents through the autophagic pathway, thereby clearing harmful substances within the cell. Lysosomal regeneration involves synthesizing new lysosomes to replace damaged ones, ensuring the stability of lysosomal numbers [36]. Previous studies have shown that TFEB and TFE3, as a crucial pair of transcription factors, play an indispensable role when lysosomes encounter damage or stress. They govern the repair mechanism of lysosomal biogenesis and secretion processes. Specifically, when lysosomes are damaged, the activity of mTORC1 is inhibited, leading to a decrease in the phosphorylation levels of TFEB and TFE3 [37, 38]. Subsequently, these transcription factors dissociate from the 14-3-3 proteins and translocate into the nucleus. Within the nucleus, TFEB and TFE3 bind to the CLEAR elements(Coordinated lysosomal expression and regulation elements) on the promoters of lysosome-related genes, thereby enhancing the transcription of genes associated with lysosomal biogenesis and secretion [39, 40]. This process not only contributes to the genesis of lysosomes but also enhances the fusion of lysosomes with the plasma membrane, allowing the release of their contents into the extracellular space, thus repairing the damaged lysosomal system. Furthermore, lysosomal damage leads to the release of calcium ions, which in turn activate calcium-dependent protein phosphatases, such as calcineurin. The role of these phosphatases is



RAGA/B/C/D:Rag GTPase;RPS6KB1:Ribosomal protein S6 kinase B1;EIF4EBP1:Eukaryotic Translation initiation factor 4E binding protein1;EIF2A:Eukaryotic translation initiation factor 2A;EIF2AK2:Eukaryotic translation initiation factor 2 AlphaKinase2;GABARAPs:GABA$_A$ receptor associated protein;G38P1:Ras-GTPase-activating protein binding protein 1; NUFIP2:Nuclear FMR1 Interacting Protein 2;LGALS8:Human GAL8;ALIX:ALG-2-interacting protein X;Galectin-3:LGALS3 protein,a type of galactoside-binding lectin

Fig. 2 The panel illustrates that lysosomal damage triggers the activation of core SG proteins such as NUFIP2 and G3BP1 through the release of Ca^{2+}. These proteins interact with ATG8s and are recruited to the damaged lysosome. ATG8 modification activates the Ragulator-RagA/B complex, inhibiting mTOR activity, which leads to phosphorylation of EIF2A and promotes SG formation. ALIX senses calcium leakage and regulates the interaction between PKR and PACT, also promoting SG formation, while galectin-3 plays a negative regulatory role. Overall, lysosomal damage promotes SG formation through mTOR regulation. NUFIP2: Nucleolar and Coiled-Body Phosphoprotein 2; G3BP1: Ras GTPase-Activating Protein SH3 Domain-Binding Protein 1; ATG8s: Autophagy-related Protein 8s; EIF2A: Eukaryotic Initiation Factor 2 A; ALIX: ALG-2 Interacting Protein X PACT: Protein Activator of the Interferon-induced Protein Kinase

to dephosphorylate TFEB and TFE3, further activating them. It is worth noting that ATG8 lipidation in lysosomes also participates in the activation process of TFEB, playing a crucial role in atypical lysosomal engulfment and microautophagy, aiding in the removal of selective lysosomal membrane proteins [41, 42]. TFEB and TFE3 are essential for lysosomal damage repair by promoting lysosomal biogenesis, enhancing lysosomal degradation activity, aiding in the clearance of pathogenic protein aggregates or pathogens, thereby maintaining lysosomal homeostasis and ensuring the normal functioning of cells.

The process of lysosomal degradation involves two key mechanisms: lysosomal engulfment and microautophagy. Severely damaged lysosomes undergo selective degradation through lysosomal autophagy, while mildly damaged ones rely on the endosomal sorting complex required for transport (ESCRT) for rapid repair. Phosphoinositide signals play a crucial role in lysosomal membrane repair by regulating intracellular calcium ion concentrations and membrane fusion to promote lysosomal membrane repair [43]. During lysophagy, damaged lysosomal membrane proteins undergo ubiquitination, subsequently attracting ubiquitin-binding autophagy adaptors such as TAX1BP1(Tax1-binding protein 1) and p62, which then connect to the autophagosome membrane. Subsequently, these structures fuse with healthy lysosomes, enabling the complete degradation of the damaged components. Additionally, V-ATPases can directly recruit the ATG12/ATG5/ATG16 complex, which subsequently facilitates the lipidation of ATG8 onto the damaged lysosomal membrane, initiating a non-canonical lysophagic process [44, 45]. Concurrently, the microautophagy mechanism also participates in the degradation of lysosomal membrane proteins. During this process, ubiquitinated lysosomal membrane proteins are recognized by the ESCRT (endosomal sorting complex required for transport) complex, triggering the microautophagy process. Mediated by the ESCRT complex, intralysosomal membrane vesicles are formed and degraded, enabling the selective clearance of specific ubiquitinated membrane proteins. Although both mechanisms involve the ubiquitination of substrate proteins, they exhibit significant differences in their execution processes. Lysophagy relies on the participation of the ATG12/ATG5/ATG16 complex for the degradation of entire damaged lysosomes, while microautophagy depends on the ESCRT complex for the selective degradation of lysosomal membrane proteins. In non-canonical microautophagy, although the ATG12/ATG5/ATG16 complex-mediated ATG8 lipidation process is also involved, triggering the formation and degradation of intralysosomal membrane vesicles, this process does not rely on the typical autophagy mechanism [46, 47]. In summary, these mechanisms act synergistically to ensure the timely and effective clearance of damaged lysosomal membrane proteins, thus maintaining the integrity of the lysosomal membrane and safeguarding the normal functioning of cells.

In addition to the aforementioned repair mechanisms, the release of Ca2 + rapidly recruits the ESCRT complex to the damaged lysosomal membrane following lysosomal injury. The ESCRT complex assembles into a helical structure on the damaged lysosomal membrane, remodels the membrane, and promotes the inward flipping of the damaged membrane into the lysosomal lumen, ultimately leading to repair via membrane scission by VPS4 (Vacuolar protein sorting 4). The regulation of ESCRT assembly is mediated by the activation of Leucine-Rich Repeat Kinase 2 (LRRK2) and the phosphorylation of Ras-Related Protein RAB-8 A [48–50].

However, researchers have discovered that lysosomal injury can still be rapidly repaired even in the absence of the ESCRT complex, suggesting the existence of other more critical repair mechanisms in cells to respond to lysosomal damage. Recent reports have employed proteomic approaches to discover that LMP triggers the phosphatidylinositol-initiated membrane tethering and lipid transport (PITT) pathway for repair, which is considered a core mechanism for lysosomal injury repair (Fig. 3). The specific mechanism involves the accumulation of PI4K2A on the damaged lysosome, leading to the production of phosphatidylinositol-4-phosphate and the recruitment of members of the ORP(Oxysterol-binding protein-related proteins) family [51, 52], promoting the transfer of phosphatidylserine and cholesterol from the endoplasmic reticulum to the lysosome, supporting rapid repair. Additionally, the lipid transfer protein ATG2 is also involved in this process, mediating rapid membrane repair through direct lysosomal lipid transport [53, 54]. The discovery of the PITT pathway holds significant importance for understanding the pathogenesis of lysosomal-related diseases, such as neurodegenerative and metabolic diseases, and provides potential new targets for the treatment of these diseases.

The relationship between lysosome damage repair mechanisms and diseases

Lysosomes and aging, neurodegenerative diseases

Lysosomal damage is a hallmark of organismal aging and the occurrence of various diseases. Research has shown that cellular lifespan depends on lysosomal function, positioning lysosomes as a central cellular hub for controlling aging [55]. Neurodegenerative diseases, as common diseases in the elderly, are a class of chronic progressive diseases that affect the brain and spinal cord, characterized by progressive cognitive impairments and behavioral changes. Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, and amyotrophic

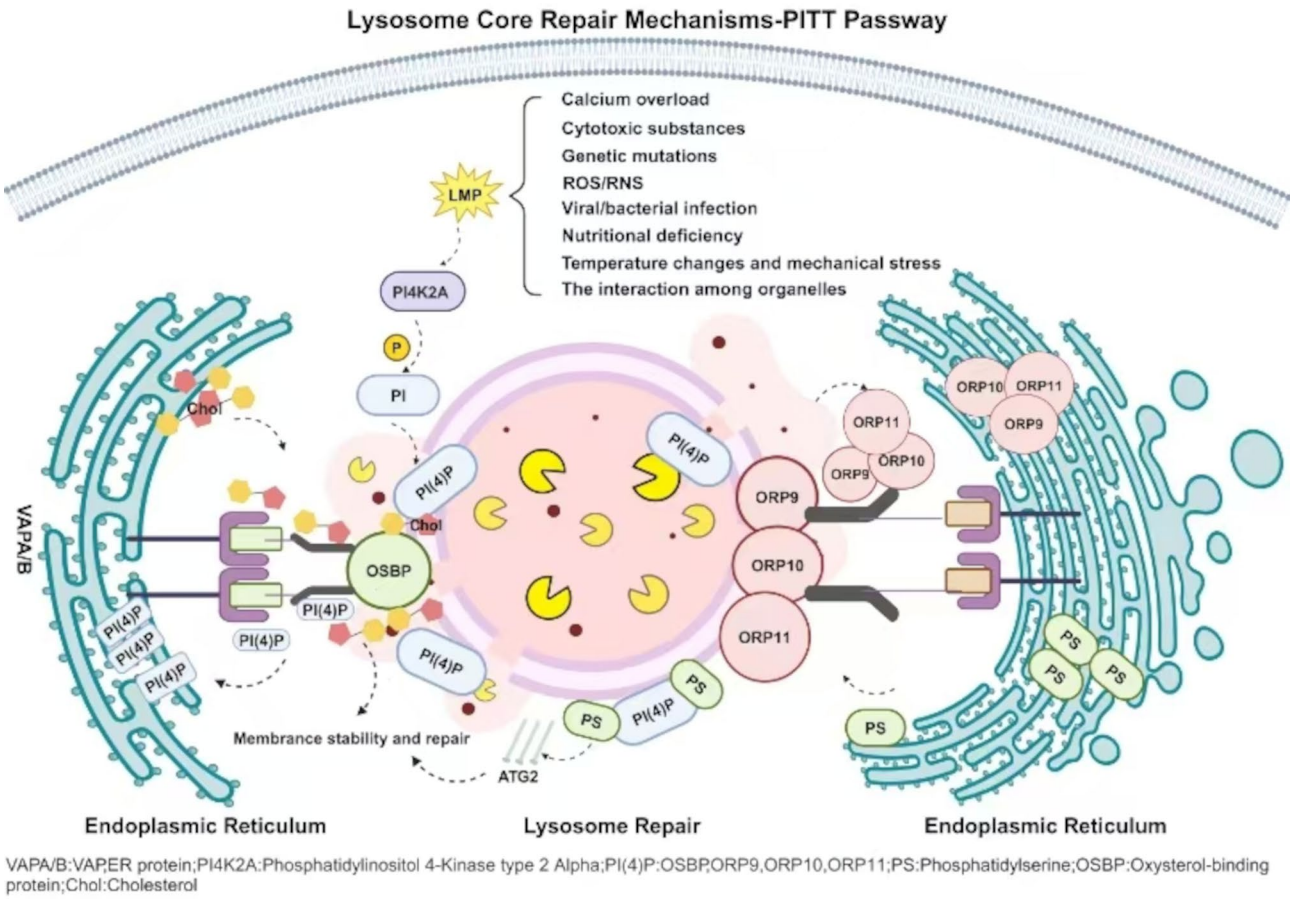


Fig. 3 The Phosphatidylinositol-Initiated Membrane Tethering and Lipid Transport (PITT) pathway, a core mechanism for lysosome repair. PITT pathway repairs lysosomes by lipid transfer from ER to damaged lysosomes via PI4P and ORP proteins. LMP caused by stressor triggers PI4K2A to generate PI4P, recruiting ORP9, ORP10, ORP11. ATG2 and ER-bound OSBP (Oxysterol-binding protein) also aid lipid transfer for rapid membrane repair. LMP: Lysosomal Membrane Permeabilization; ROS/RNS: Reactive Oxygen/Nitrogen Species; ER: Endoplasmic Reticulum

lateral sclerosis are typical representatives of this group of diseases [56, 57]. These diseases not only severely impact patients' quality of life but also impose a heavy burden on society and the economy. previously mentioned SGs - these membrane-less cytoplasmic ribonucleoprotein (RNP) granules - contain translationally stalled RNA and play a protective role for mRNA and long non-coding RNAs (lncRNAs) [58]. SGs are associated with the pathophysiology of neurodegenerative diseases such as Alzheimer's disease and contain various RNA-binding proteins (RBPs) relevant to AD progression. Although SGs are transient structures, chronic stress can lead to their sustained formation, resulting in pathological SGs, impairing cellular RNA metabolism, and promoting the abnormal aggregation of AD-related proteins [59]. Additionally, reports indicate significant alterations in cholesterol metabolism in aging cells, specifically manifested as enhanced expression of the cholesterol transport protein ABCA1(ATP-binding cassette subfamily A member 1). As a key protein for cholesterol efflux, ABCA1 leads to the accumulation of cholesterol within lysosomes. The accumulation of cholesterol within lysosomes impacts the formation of microdomains, activating the mTORC1 signaling pathway. This activation helps inhibit the occurrence of the senescence-associated secretory phenotype (SASP), suggesting a potential protective mechanism. However, excessive cholesterol accumulation might disrupt cellular homeostasis, the exact impact depends on factors like the extent of cholesterol accumulation and the cell type affected, thus, regulating lysosomal cholesterol levels via drugs can influence age-related phenotypes like osteoarthritis [60]. Besides, in Alzheimer's disease, lysosomal damage can lead to the leakage of tau protein fibers, subsequently causing damage and death of nerve cells. In neurodegenerative diseases, abnormal lysosomal function is directly linked to the progression and deterioration of the diseases [56, 61]. The reasons for the impairment of the autophagic-lysosomal pathway are complex, potentially involving genetic variations, environmental factors, cellular aging, and disease characteristics. These factors may lead to fusion barriers between autophagosomes and lysosomes, hindering the degradation process,

causing intracellular substance accumulation, and exacerbating neuronal damage [62, 63]. Therefore, restoring autophagic-lysosomal function is crucial for treatment. In Alzheimer's disease, the accumulation of beta-amyloid proteins is a significant pathological feature of the disease. When lysosomes function properly, they break down and remove waste proteins, maintaining cellular health. However, when lysosomal function is impaired, the creation of autophagic-lysosomes is also negatively impacted [64, 65]. This means that the cell's ability to clear out harmful proteins and other waste materials is compromised, potentially leading to the accumulation of these substances within the cell. Such accumulation can disrupt normal cellular functions and contribute to various disease states, including neurodegenerative diseases and other age-related conditions [66, 67]. One of the mechanisms underlying early-onset Parkinson's disease is the Parkin-mediated mitochondrial autophagy pathway. This pathway removes damaged mitochondria from cells, and its dysfunction can lead to the progressive accumulation of damaged mitochondria, ultimately resulting in the death of dopaminergic neurons [68]. Recent studies have shown that ROCK (Rho-associated protein kinase) can serve as a molecular switch in the Parkin-mediated mitochondrial autophagy pathway. The use of ROCK inhibitors can enhance Parkin-mediated mitochondrial autophagy, thereby improving relevant phenotypes of PD in vivo, potentially becoming a target for Parkinson's treatment [69]. Also, recent research has found a close relationship between the formation of lipid droplets (LD) and autophagy. LDs are selectively autophagically degraded through lysosomes, a process known as lipophagy. Lipophagy is an important process in the central nervous system (CNS). The accumulation of LDs exacerbates the development of AD pathology and lysosomal dysfunction, thereby affecting autophagy [70].

Impaired lysosomal acidification function is considered a significant driving factor in the occurrence and progression of neurodegenerative diseases [71]. The acidification of lysosomes depends on the V-ATPase proton pump and ion channels on the lysosomal membrane, such as TRP (Transient receptor potential), TPC (Two-pore channel), TMEM175 (Transmembrane protein 175), and chloride-proton exchange proteins. These collectively regulate the exchange of Ca2+, Na+, K+, and Cl- ions, maintaining lysosomal acidification [72]. In recent years, there has been increasing attention on the acidification function of lysosomes. In addition to its association with neurodegenerative diseases, it has been reported that the restoration of lysosomal acidification defects can rescue autophagy and metabolic dysfunction in non-alcoholic fatty liver disease [73]. Studies have shown that lysosomal acidification dysfunction in the central nervous system leads to reduced degradation efficiency, resulting in the formation of under-acidified autolysosomes, which are associated with early neurodegenerative changes and the accumulation of toxic protein aggregates. The V-ATPase, as a multimeric enzyme complex, pumps protons into lysosomes, with the V1 domain playing a critical role [10, 72]. Due to the impairment of vacuolar-type ATPases and ion channels on the lysosomal membrane by various genetic factors, they are unable to maintain the internal acidic environment properly. Optimal lysosomal acidification at pH 4.0–5.0 is crucial for the fusion with autophagosomes and maintaining normal lysosomal function [72, 74] including the maintenance of hydrolase activity, clearance, degradation of "waste," and organelle biogenesis. PH abnormalities prevent the clearance of abnormal large protein aggregates and organelles, leading to the abnormal accumulation of proteins and lipids within cells [75], affecting the survival of non-dividing neurons, thereby causing damage and death of nerve cells [76], impacting their central role as signaling hubs and controllers of cellular processes [21, 77].

In addition, lysosomes are involved in the energy metabolism and ion balance of neurons. Disruption of these processes in neurodegenerative diseases may lead to abnormal neuronal function and death [78]. Lysosomes are organelles responsible for the storage and balance of Ca2+, with channels and transport proteins regulating the Ca2 + homeostasis of lysosomes and the entire cell [79, 80]. Dysfunction of lysosomes is associated with lysosomal storage diseases, metabolic disorders, and neurodegenerative diseases [81]. Recent studies have shown that the exchange of Ca2 + between lysosomes and the endoplasmic reticulum is crucial for neuronal health. The TRPML1(Transient receptor potential mucolipin 1) channel [82] plays a key role in amyotrophic lateral sclerosis, and its activation can promote autophagy, providing a new avenue for treatment [83, 84]. Lysosomes maintain cellular homeostasis by interacting with other organelles [85, 86], but this homeostasis may be disrupted in disease states, further exacerbating neuronal damage. Besides, recent studies have revealed an important proton dissipation pathway within lysosomes, providing molecular targets for regulating pH-dependent lysosomal function and related pathologies. LyPAP (Lysosomal proton-activated pathway), encoded by the TMEM175 gene, is a proton-activated selective channel crucial for maintaining the lysosomal H+ 'leak' current. This channel is most active during lysosomal hyperacidification, helping to prevent further acidification and maintain the optimal pH range for lysosomal enzyme activity. Cells lacking TMEM175 exhibit lysosomal hyperacidification and impaired protein degradation due to the absence of this essential proton efflux mechanism. These impairments can be restored by modulating lysosomal pH through interventions that enhance proton

efflux or inhibit excessive proton influx, highlighting the critical role of TMEM175 in lysosomal homeostasis and cellular health. Variants of TMEM175 associated with susceptibility to Parkinson's disease result in reduced LyPAP current and lysosomal hyperacidification [87, 88]. By activating lysosomal function and restoring its degradation capacity, we hope to slow down disease progression, reduce neuronal damage, and improve patients' quality of life.

Lysosomes and tumors

In cancer cells, the generation and autophagy process of lysosomes are enhanced [21, 89] to support their metabolic demands for proliferation in environments relatively deficient in nutrients and oxygen. However, this enhanced lysosomal function comes at a cost, as cancer cells themselves are more susceptible to lysosomal membrane permeabilization, leading to cell death [90]. Studies have found that abnormal activation of classic oncogenes such as Kras and Myc can increase the expression of lysosome-related genes [91, 92]. Cancer cells enhance metabolism by adjusting the quantity, localization, and activity of lysosomes to meet their needs for growth and proliferation. This change is associated with overexpression of lysosomal proteins and lysosome-associated proteins, such as lysosomal catalase, lysosomal glucosidase, and kinases. Some types of cancer, such as pancreatic cancer, renal cell carcinoma, melanoma, and breast cancer, have been found to exhibit overexpression of MiT/TFE (Microphthalmia-associated transcription factor/Transcription factor EB) genes [93, 94]. By enhancing clearance pathways of nutrients, such as autophagy and endocytosis, cancer cells can compete for limited food resources and survive in harsh environments, such as tumors with poor vascularization or tumors undergoing radiation or chemotherapy [95, 96]. The nutrients brought by these pathways activate the mTOR signaling pathway [97, 98], promoting the synthesis of amino acids, glucose, nucleotides, fatty acids, and lipids, all of which are essential for cell proliferation. Abnormal excessive activation of catabolic and anabolic metabolic pathways drives the metabolism and proliferation of cancer cells. Furthermore, tumor cells also induce lysosomal release of contents into the extracellular space, and these lysosomal changes have significant impacts on the proliferation, migration, invasion, and resistance to radiation and chemotherapy of cancer cells [99–101].

In addition, lysosomes are involved in the degradation of intracellular pathogens and foreign substances, impacting immune evasion of tumor cells, as well as drug metabolism and degradation, closely related to drug resistance in tumor cells. Importantly, lysosomes participate in the reprogramming of intracellular metabolic pathways, exerting profound effects on energy production and growth of tumor cells. TFEB, as a key regulatory factor of lysosomal function and considered an oncogene in various cancers, works alongside other members of the MiT/TFE family, these findings underscore the significant role of lysosomes in cancer development and highlight their importance as potential therapeutic targets [86]. Inactive EGFR interacts with lysosomal membrane protein LAPTM4B on the endosome, stabilizing each other and recruiting the Sect. 5 subcomplex. These molecules are crucial for both basal and starvation-induced autophagy. LAPTM4B and Sect. 5 promote the association of EGFR with autophagy inhibitor Rubicon, thereby initiating autophagy. LAPTM4B facilitates the role of inactive EGFR in autophagy, contributing to tumor metabolism regulation and cell survival [102]. Studies have shown that the viscosity of lysosomes in cancer cells is higher than that of normal cells, and the lysosomal pH in cancer cells (3.8–4.7) is lower than that in normal cells (4.5-6.0). The higher viscosity and lower pH of lysosomes in cancer cells have the potential to serve as cancer biomarkers [103]. Additionally, a viscosity-sensitive, lysosome-targeted near-infrared fluorescent probe called PYATT was reported this year. The fluorescence spectrum of PYATT is significantly influenced by viscosity, with an approximately 190 nm Stokes shift. Due to its excellent photostability, low cytotoxicity, and high fluorescence quantum yield, PYATT demonstrates great potential in the field of cell imaging. Given that the viscosity of tumor cells is higher than that of normal cells, the fluorescence intensity of PYATT is correspondingly enhanced in tumor cells, enabling tumor visualization. Besides, the viscosity-dependent properties of PYATT in lysosomes are of significant importance for the early diagnosis and treatment of tumors [104]. Recent research has utilized the intrinsic properties of nanoparticles to construct a selective, safe, and effective lysosomal alkalizing agent. Composed of an iron oxide core, it generates hydroxyl radicals (•OH) in cancer cell lysosomes in the presence of H + and hydrogen peroxide, along with cerium oxide satellites that capture and convert •OH to hydroxide ions. Studies have shown that this alkalizing agent effectively inhibits local and systemic tumor growth and metastasis in mice [105].

It is worth noting that recent studies have revealed a long-chain non-coding RNA - Lysosomal Cell Death Regulator (LCDR), which plays a crucial role in lung cancer cell survival through histone acetylation regulation. The specific mechanism involves LCDR binding with heterogeneous nuclear ribonucleoprotein K (hnRNPK) to jointly regulate the stability of lysosome-associated membrane protein 5 (LAPTM5) transcripts. This regulatory process ensures the integrity of lysosomal membranes, thereby maintaining normal lysosomal function. Depletion of LCDR, hnRNPK, or LAPTM5 increases lysosomal membrane permeability, leading to lysosomal cell death

and ultimately triggering apoptosis. Cysteine proteases are enzymes that break down proteins and are involved in various cellular processes, including cell death. Cysteine protease inhibitor B is a compound that can block the activity of cysteine proteases. In this context, the overexpression of LAPTM5 or the use of cysteine protease inhibitor B can partially counteract the impact of the LCDR/hnRNP K/LAPTM5 axis on lysosomal cell death. This suggests that the LCDR/hnRNP K/LAPTM5 axis plays a crucial role in regulating lysosomal function and that modulating this axis can influence cell survival. Additionally, nanoparticle-mediated systemic delivery of short interfering RNA targeting LCDR can effectively inhibit tumor growth in lung adenocarcinoma (LUAD) and induce cell death, providing a new strategy for lung cancer treatment [106, 107].

In cancer treatment, multidrug resistance is a key issue, with lysosomes playing a crucial role. Chemotherapeutic drugs accumulate in lysosomes due to the pH difference between lysosomes and the cytoplasm. These drugs are sequestered in lysosomes, including cisplatin [108], sunitinib [109], amphotericin B [110] and colchicine [111]. Cancer cells can induce the expression of drug efflux transporters, pumping drugs into lysosomes [112, 113], such as ABC transporters P-glycoprotein and A3 [114]. Drug sequestration prevents them from reaching their intracellular targets, reducing lysosomal activity. To compensate, cells activate TFEB-mediated lysosomal biogenesis, exacerbating drug resistance [115]. Lysosomal exocytosis also contributes to drug resistance, as evidenced in various cancers [116–118]. LAMP1, as a lysosomal marker, can be used to detect the formation of autophagic lysosomes, and in tumor cells, LAMP1 is also involved in the autophagic process [119, 120]. Changes and dysfunction of lysosomes play a crucial role in cancer cells evading attacks from the host immune system.

Lysosomal degradation is not only responsible for antigen processing but also controls the presentation of MHC-I on the cell membrane. It has been reported that the reduced surface expression of MHC-I in pancreatic ductal adenocarcinoma (PDAC) cells is due to MHC-I degradation through lysosome-dependent autophagy. In PDAC cells, co-localization of MHC-I with autophagosomes and lysosomes can be observed, and in mouse models, inhibiting autophagy can restore MHC-I levels and promote T cell responses [121]. Also, the loss or blockade of tumor cell co-stimulatory molecules is one of the important mechanisms for tumor immune evasion, as lysosomes are not only responsible for the degradation of immune checkpoints like CTLA-4, PD-L1, and CD47 but also for their membrane transport and presentation. CMTM6 and PD-L1 co-localize in the cell membrane and intracellular vesicles, inhibiting the lysosomal degradation of PD-L1, allowing PD-L1 to interact with PD-1 on T cells, thereby evading immune protection mediated by T cells. Additionally, lysosomes are involved in regulating the tumor microenvironment [122]. The tumor microenvironment is a complex ecosystem, including tumor cells, immune cells, and extracellular matrix. Lysosomes degrade the extracellular matrix and modulate the activity of immune cells, altering the structure and function of the tumor microenvironment, further impacting tumor growth and invasion [123, 124].

Lysosomes and inflammation and immune regulation

Inflammation and immune regulation are two core mechanisms by which the body defends against external pathogens and maintains internal homeostasis. Lysosomal autophagy plays a complex role in the process of inflammation. It can participate in anti-inflammatory autophagy by tagging "autophagic cargo" through ubiquitination, etc., identifying them as SLRs (Stress-like responses) for aggregation autophagy and mitophagy [125, 126], and restricting the inflammatory reaction by eliminating endogenous damage-associated molecular patterns [127], oxidative stress mediators, and inflammatory complexes [128–130].

In addition, studies have shown that autophagy can inhibit the activation of various inflammatory signaling pathways through different mechanisms Specifically, the ATG5-ATG12 (Autophagy-related protein 5-autophagy-related protein 12) complex can bind to pattern recognition receptors (PRRs) such as retinoic acid-inducible gene 1 (RIG-1), thereby inhibiting the RIG-1-like receptor (RLR) signaling pathway and subsequently down-regulating the secretion of type I interferon (IFN). On the other hand, ATG9 inhibits the dsDNA-induced IFN signaling pathway by regulating the activity of TBK1 (TANK-binding kinase 1). The activation of the nuclear factor-kappa B (NF-κB) signaling pathway is a key step in inflammation mediated by most pathogens. Interestingly, the autophagy-regulating protein RUBICON can further control the inflammatory response by down-regulating NF-κB activity through inhibiting the formation of the B-cell lymphoma 10 (BCL-10) complex [131]. In addition to directly regulating signaling pathways, autophagy can also inhibit the generation of interleukins (including IL-1β, IL-1α, and IL-18) by clearing damaged mitochondria, which are known to release pro-inflammatory molecules such as reactive oxygen species (ROS) and oxidized mitochondrial DNA when injured. These released substances can trigger the NLRP3 inflammasome and promote the secretion of pro-inflammatory cytokines. By removing damaged mitochondria through the autophagy process, cells can reduce the levels of these pro-inflammatory molecules, thereby inhibiting the production of interleukins and dampening the inflammatory response [132, 133]. While clearing pathogens,

dangerous molecules such as oxidized mitochondrial DNA can be released into the cytoplasm when lysosomes are damaged, activating inflammasomes and promoting the inflammatory response. Similarly, TBK1, as a key molecule regulating lysosomal autophagy, is involved in the formation and maturation of autophagosomes and regulates lysosomal damage repair, thereby affecting the inflammatory response [134]. This dual role makes the balance between lysosomal autophagy and inflammation crucial [126, 135].

In immune cells, lysosomal autophagy is crucial for the normal development, differentiation, and function of cells. High levels of lysosomal autophagy help immune cells exhibit anti-inflammatory activity. The role of lysosomes in immune regulation is increasingly being recognized, as they not only provide essential nutrients and energy to immune cells but also support the activity and function of immune cells by degrading pathogens and extracellular matrix. Furthermore, lysosomes are involved in the signaling and metabolic regulation of immune cells, ensuring that immune cells can respond rapidly and accurately to challenges from external pathogens [126]. Immunity is influenced by lysosomal activity in dendritic cells (DCs) and macrophages [136, 137]. In innate immunity, bacteria are internalized and degraded in lysosomes through phagocytosis. If bacteria escape into the cytoplasm, the autophagic mechanism captures and delivers them to lysosomes. Additionally, TLRs (Toll-like receptors) on the lysosomal membrane recognize microbes and host ligands, triggering pro-inflammatory signals [138]. In adaptive immunity, antigen peptides are presented to CD4 + T cells via major histocompatibility complex class II (MHC-II) molecules. The degradation and denaturation of phagosomes and lysosomes induced by TLR4 signaling are crucial for antigen presentation. Autophagy plays opposing roles in MHC-II and MHC-I presentation, promoting MHC-II presentation but inhibiting MHC-I presentation [94, 139, 140]. Similarly, lysosomes play a significant role in the immunosuppressive function of regulatory T cells (Tregs) [141]. Treg cells play a crucial role in maintaining immune homeostasis and controlling immune tolerance, and lysosomes ensure the proper function of Treg cell suppression by maintaining the homeostasis of the endolysosomal system and regulating the activation of the amino acid signaling-dependent mTORC1 pathway and cell metabolism [142, 143]. This discovery not only reveals the crucial role of lysosomes in regulating immune responses but also provides new therapeutic strategies for enhancing anti-tumor immunity. In addition, transcription factor EB (TFEB), a key controller of autophagy and lysosomal biogenesis, is increasingly recognized for its role in modulating the inflammatory immune response in organisms [144]. TFEB comprehensively regulates the immune reactions in organisms by influencing lysosomal biogenesis and directly controlling the transcription of immune-related genes [145, 146].

Lysosomes and regenerative medicine

Regenerative medicine, as a frontier field in modern medicine, aims to repair damaged tissues and organs, bringing new hope to patients. The study of lysosomal mechanisms is an essential part of regenerative medicine. Firstly, lysosomes are involved in the degradation and remodeling of the extracellular matrix. In regenerative medicine, especially in the field of tissue engineering, the structure and function of the extracellular matrix are crucial for the formation and function of new tissues. Literature reports that during the molting period of nematodes, when the extracellular matrix of cuticle undergoes remodeling, lysosomes within epidermal cells are specifically activated, promoting the degradation and recycling of cuticle components, aiding in the synthesis of new cuticle, and completing the molting process. Changes in adhesion factors between the cuticle and epidermal cells during the molting period activate the expression of V-ATPase and the function of lysosomes through the transcription factors STA-2 and ELT-3. This study reveals a signaling pathway that selectively activates lysosomes, with its effects spanning from the extracellular matrix to the nucleus, promoting extracellular matrix remodeling and larval development [147]. Additionally, lysosomes can degrade aging extracellular matrix components by releasing hydrolytic enzymes, providing space for new matrix components and promoting cell migration and adhesion, thereby aiding in tissue regeneration and repair.

New mechanisms of lysosomal regulation of stem cell differentiation and regeneration

Studies have shown that lysosomes are central to stem cell regulation [148–151], with their surface serving as a hub for metabolic signaling pathways like mTORC1 and AMPK, which are vital for stem cell differentiation [152–154]. Stem cells are key elements in regenerative medicine. It has been reported that the lysosomal activity of long-term hematopoietic stem cells (LT-HSCs) is mainly regulated by the TFEB and MYC: TFEB enhances lysosomal activity to promote receptor degradation, thereby inhibiting the activation process of LT-HSCs; while MYC inhibits lysosomal breakdown metabolism, driving biosynthesis, and activating LT-HSCs.When the body senses a demand, the expression of the environmental sensing receptor TfR1 in LT-HSCs increases, and the MYC protein weakens lysosomal activity by inhibiting the expression of lysosomal-related genes, thereby promoting the differentiation of LT-HSCs into red blood cells; simultaneously, TFEB enhances lysosomal activity by promoting

the expression of lysosomal-related genes, allowing LT-HSCs to better maintain their quiescent state, self-renewal, and lineage differentiation capability [155, 156]. This study reveals the core role of lysosomal transcriptional regulatory mechanisms in the regulation of stem cells, providing a new direction for the field of regenerative medicine. By regulating the activity and function of lysosomes, we can influence the differentiation direction and efficiency of stem cells, thereby promoting the regeneration process of specific tissues. Furthermore, lysosomes are involved in the regulation of cell apoptosis and autophagy processes. In regenerative medicine, cell apoptosis and autophagy are important mechanisms for maintaining tissue homeostasis and removing damaged cells. Lysosomes contribute to clearing dead or damaged cells and providing a favorable environment for the growth and differentiation of new cells.

Currently in regenerative medicine, researchers are dedicated to repairing damaged nervous systems through stem cell therapy to treat neurodegenerative diseases [133, 157]. Recently, the Institute of Zoology, Chinese Academy of Sciences, revealed that endocytic lysosomes regulate the selective translation of transcripts through asymmetric inheritance, playing a role in maintaining stemness. Additionally, it was found that differentiated daughter cells do not inherit lysosomes; by enhancing autophagy to generate newly formed autophagic lysosomes, cell fate reshaping can be promoted [158]. Similarly, lysosomes can regulate the activity of nuclear transcription factors such as TFEB, influencing gene expression and thereby determining the fate of stem cells. Moreover, by degrading metabolites such as amino acids and responding to epigenetic modifications [159], lysosomes play an indispensable role in cell metabolism and signal transduction [160]. They can also form membrane contact sites with other organelles such as mitochondria and endoplasmic reticulum, collectively regulating metabolic and signal transduction processes [161, 162]. Furthermore, lysosomes degrade cellular components through autophagy, which help maintain the stability of the internal stem cell environment. For mesenchymal stem cell therapy [163], lysosomal damage may lead to ineffective survival and differentiation of MSCs after transplantation [164]. In conclusion, the activity of lysosomes is closely related to the fate of stem cells, and in-depth study of their regulatory mechanisms is of great significance for understanding stem cell function and therapy.

In addition to cell therapy, cell reprogramming is a technique in regenerative medicine that transforms one type of cell into another type of cell. Lysosomes play an important role in the process of cell reprogramming, such as by regulating processes like intracellular substance degradation and signal transduction. For both drug therapy and biomaterial aspects in regenerative medicine, studying lysosomal damage repair mechanisms can help develop new drug treatment strategies for diseases related to lysosomal damage and aid in designing and developing biocompatible biomaterials to promote cell survival and function.

The regulatory mechanism of lysosomes in cardiac cell regeneration

Regenerative medicine provides effective treatment strategies for cardiac injury repair through the comprehensive use of cell therapy, artificial assistive devices, and drug therapy. Cardiovascular diseases, especially ischemic cardiomyopathy, have become one of the most serious threats to human health today. In such heart diseases, the impaired autophagy-lysosome pathway (ALP) plays a crucial role.

Studies have found that damaged cardiac TFEB signaling plays a crucial role in cardiac protein-related diseases, and TFEB overexpression can protect cardiac cells by improving ALP activity. The specific mechanism is that when TFEB expression is abnormal, the autophagy process is inhibited, leading to an increase in protein aggregates, which in turn causes damage to cardiac cells; conversely, overexpression of TFEB can significantly improve ALP activity, increase autophagic flux, thereby reducing protein toxicity, and protecting cardiac cells from damage [165]. Additionally, LAMP-2, as a key protein maintaining lysosomal integrity and function, also plays an indispensable role in the process of cardiac cell repair. It promotes the fusion of lysosomal vesicles with endosomes, maintains lysosomal pH and stability, and is crucial for lysosomal function [166]. In the autophagy process, LAMP-2 participates in the fusion of autophagosomes with lysosomes, regulates the rate of autophagic flux, further promoting the repair and regeneration of cardiac cells [167, 168]. AdipoRon therapy enhances LAMP2 expression, promotes autophagosome formation and clearance, reduces infarction, and improves heart function by activating the AMPK and antioxidant pathways. AMPK inhibition affects autophagosome formation but does not affect LAMP2 expression and clearance. Superoxide anion scavengers have similar effects, but do not have an additive effect with AdipoRon [169]. However, it is worth noting that mutations in the LAMP2 gene may lead to primary LAMP-2 deficiency, resulting in rare X-linked vacuolar cardiomyopathy and myopathy, known as Danon disease. This disease significantly affects the health of the heart and muscles, further highlighting the importance of LAMP-2 in the repair and regeneration of cardiac cells [170].

Myocardial ischemia/reperfusion injury (MI/R) is a major challenge in the field of cardiovascular medicine, where the damage and repair processes of cardiac cells

are particularly complex [171]. Regenerative medicine has delved into the key role of lysosomes in exploring strategies for cardiac cell repair, highlighting the crucial importance of lysosomal function in the repair of cardiac cells.

Recent studies have found that autophagy, a critical cellular homeostasis maintenance system, plays an important role in MI/R injury [172, 173]. Lysosomal autophagy in myocardial injury repair is a double-edged sword. During the ischemic phase, lysosomes, activated through the AMP-activated protein kinase pathway, clear misfolded proteins and damaged mitochondria that induce cardiomyocyte death, thereby exerting a protective effect on the myocardium. Studies also suggest that Doxorubicin not only affects the survival capacity of cardiac cells by inhibiting the expression of transcription factor EB [174] but also hampers autophagic flux by impairing lysosomal acidification [175].

However, during the reperfusion phase, autophagy induction relies on Beclin-1 rather than AMPK. At this stage, autophagy is activated, but it may excessively deplete intracellular resources, exacerbate cell damage, and lead to the formation of autophagic bodies, causing harm to the myocardium. Additionally, autophagosome formation in diabetic cardiac cells is suppressed, impairing damaged clearance and affecting the autophagic process in myocardial ischemia-reperfusion (MI-R) injury [176, 177]. Concurrently, hypoadiponectinemia damages autophagic flux, exacerbating MI-R injury in diabetes. Recent studies have revealed the protective role and regulatory mechanism of lysosomal membrane protein LAPTM4B in myocardial ischemia/reperfusion injury (MI/R), further elucidating the significant role of lysosomes in myocardial injury repair and providing new theoretical basis for developing novel strategies for cardiac repair therapy. The specific mechanism is that during the reperfusion phase, the lysosomal function of cardiomyocytes decreases. This decrease in lysosomal function leads to the blockage of autophagic flux. As a result, autophagic bodies accumulate within the cells and ultimately cause massive cardiomyocyte death. LAPTM4B is crucial for maintaining lysosomal function, and its downregulation can exacerbate MI/R injury. Overexpression of LAPTM4B can reverse these phenotypes, but its effects can be abolished by lysosomal function inhibitors. LAPTM4B inhibits the activation of the mTORC1 complex, promotes TFEB nuclear translocation, maintains lysosomal function, and enhances the resistance of cardiomyocytes to MI/R injury. Therefore, maintaining lysosomal function is crucial for alleviating MI/R injury [178]. Similarly, the differentiation capacity of stem cells is crucial for the formation of new myocardial tissue during the process of cardiac cell repair. Lysosomes regulate the direction and efficiency of stem cell differentiation, providing strong support for the regeneration of cardiac muscle tissue.

In conclusion, lysosomes play crucial roles in various biological processes and diseases. They are involved in neurodegenerative diseases, where their specific functions and repair mechanisms offer potential targets for treatment. In cancer, lysosomes influence immune regulation, presenting opportunities to enhance anti-tumor immunity or inhibit immune evasion. Their role in inflammation and immune regulation is also significant, affecting the body's defense capabilities and homeostasis. Furthermore, lysosomes are indispensable in cardiac cell repair, with regenerative medicine research pointing to new therapeutic strategies for heart disease patients. Overall, understanding lysosome functions and their implications across different diseases is vital for developing innovative treatments. Future research should focus on deepening our knowledge of lysosome-related mechanisms and exploring interdisciplinary approaches to leverage these insights for improved health outcomes.

Lysosome-targeted treatment strategies: advances in preliminary research

The prospect of using lysosomes in disease treatment is promising. Lysosomal damage is closely related to the occurrence and development of various diseases. By regulating the function of lysosomes, we can intervene in the progression of diseases to achieve therapeutic goals. For example, through research on lysosomal damage repair mechanisms, we can develop lysosomal activators or targeted drugs to enhance lysosomal function or regulate its activity, thereby improving the therapeutic effects of diseases.

Breakthrough in targeting lysosomes for Alzheimer's disease treatment: prospects of the DAT-CDK9-TFEB pathway and LH2-051

In recent years, Alzheimer's disease treatment has faced challenges, and researchers have focused on the potential role of lysosome generation in AD. They first revealed the new mechanism of DAT-CDK9-TFEB regulating lysosome generation, providing new avenues for treatment. In this mechanism, inhibiting the function of dopamine transporter protein (DAT) can activate the pathway and promote lysosome generation. The novel small molecule compound LH2-051 binds to DAT, alters DAT distribution, affects CDK9 activity, thereby promoting TFEB nuclear translocation and lysosomal biogenesis. This process does not rely on traditional pathways, revealing a new mechanism of neurotransmitter transporter. In AD mouse models, LH2-051 reduces plaque deposition and improves learning and memory, indicating that regulating the DAT-CDK9-TFEB pathway may be an effective treatment method [179–182].

Exploration of the integrated application and case studies of lysosome-targeted anti-tumor therapies

Lysosome-targeted treatment strategies, as an important research direction in the current field of cancer treatment, have made significant progress in preliminary research. The core of this strategy lies in disrupting lysosomal membranes, releasing lysosomal enzymes, initiating cell death pathways, and thereby enhancing anti-tumor effects. In practical applications, the combination of lysosomal membrane disruptors with different types of drugs has shown significant potential. First, the combination with chemotherapy drugs can significantly enhance the sensitivity of tumor cells to drugs, effectively reversing drug resistance [183]. Secondly, by regulating the autophagy process, the combined use of autophagy inhibitors can further enhance the anti-tumor effect of lysosomal membrane disruptors. In addition, the combination with microtubule-targeting drugs, such as vincristine, can synergistically combat tumors [184]. Additionally, the combined use of targeted drugs, such as lapatinib, can inhibit tumor angiogenesis, working together with lysosomal membrane disruptors to exert a potent anti-tumor effect. Lastly, the combined use of drugs that inhibit lysosomal acidification with lysosomal membrane disruptors, such as the combination of nintedanib with chloroquine or bafilomycin A1, can significantly enhance the anti-tumor effect [185, 186].

These explorations not only validate the feasibility of lysosome-targeted treatment strategies but also provide new ideas and methods for cancer treatment. Through continuous in-depth research and practice, it is believed that lysosome-targeted treatment will play an increasingly important role in cancer treatment in the future [187–189].

The diversity and emerging therapeutic approaches of lysosome-targeted treatment strategies

In addition to the previously discussed combination of lysosomal membrane disruptors with other drugs, various emerging strategies have emerged for the treatment of lysosome-related diseases. Among them, using gene editing technology to repair mutations in lysosome-related genes provides new possibilities for disease treatment [190–192]. These strategies not only hold promise for improving patients' quality of life and prognosis but also pave the way for the treatment of lysosome-related diseases.

Firstly, enzyme replacement therapy has shown potential in the treatment of lysosomal storage diseases [193]. Through modification by the Golgi network, extracellular enzymes are absorbed and delivered to lysosomes, providing a potential for enzyme replacement therapy. However, despite the important role of recombinant enzymes and dosing strategies in enzyme replacement therapy, we still face the significant challenge of achieving effective systemic drug delivery across the blood-brain barrier. Therefore, future research needs to focus on optimizing dosing strategies to improve treatment outcomes.

Secondly, regulating autophagy is also an important direction in the treatment of lysosome-related diseases. Autophagy plays a key role in the development of various diseases, especially in the regulation of macrophage phenotypes. Although mTOR serves as a major target protein in the autophagy pathway, its inhibition can induce autophagy, but existing evidence is insufficient to prove that the anti-atherosclerotic effect of mTOR inhibitors is entirely achieved through autophagy. On the contrary, the anti-inflammatory effect may play a more important role in this process. Therefore, when administering autophagy inhibitors or inducers, researchers must be cautious, and the drugs used should be targeted [194, 195].

Additionally, inhibiting tissue proteases has shown potential therapeutic value. Tissue proteases released by tumor cells and TAMs (Tumor-associated macrophages) can promote the malignant phenotype of tumors, such as invasion and resistance to chemotherapy. However, the efficacy of tissue protease inhibitors is not always ideal, which may be due to their side effects and non-specific inhibition. Therefore, to improve treatment outcomes, it may be necessary to use specific or local administration methods and combine with other therapies, such as radiotherapy [196, 197].

Lastly, TLR agonists and other selective drugs offer new hope for immunotherapy. Although lysosome-targeted drugs are under development, lysosome intervention measures in clinical trials are still limited. Currently, the side effects and target effects of these drugs are the main limitations to their application. Therefore, the development of drugs that can temporarily and controllably inhibit or activate lysosomes may help reduce side effects and maximize the preservation of their physiological functions [198]. In summary, the diversity of lysosomal targeted therapeutic strategies and emerging treatment approaches offer promising prospects for the treatment of diseases. Through continuous exploration and optimization of these strategies, we aim to bring better treatment outcomes and improved quality of life to patients with lysosome-related diseases.

Summary: interdisciplinary research on lysosome damage repair mechanisms and their prospects in disease treatment

Lysosomes, as crucial cellular organelles, has significantly advanced our understanding of cellular homeostasis and disease mechanisms. From their initial discovery to the exploration of their complex functions and repair mechanisms, lysosomes have emerged as central players

in various biological processes and disease pathologies. As the central organelles responsible for cellular degradation and recycling, play a pivotal role in maintaining cellular homeostasis. Recent advances have highlighted their involvement not only in metabolic regulation but also in cancer, inflammation, immune response, and tissue regeneration et al. Understanding lysosome damage and repair mechanisms has thus become a critical focus across multiple disciplines, offering new insights into disease pathogenesis and therapeutic development.

Biological research has elucidated the fundamental aspects of lysosome damage, including its causes such as oxidative stress, drug effects, and genetic mutations, and the subsequent repair processes involving membrane repair and hydrolase regeneration. These findings have deepened our comprehension of cellular equilibrium mechanisms and laid the groundwork for addressing lysosomal disorders.In the medical field, the insights gained from lysosome injury repair mechanisms are being translated into clinical applications. Researchers are developing strategies to modulate lysosomal function using activators and targeted drugs, aiming to enhance therapeutic outcomes. Gene editing technologies are also being harnessed to correct mutations in lysosomal genes, opening up innovative treatment avenues for lysosomal disorders.Chemistry and materials science contribute to this interdisciplinary effort by creating materials designed for lysosome repair. Functional materials like lysosome-targeted nanomedicines and high molecular weight materials for membrane restoration are being developed to effectively repair lysosomal damage. These materials not only aid in understanding lysosome structure and function but also provide novel tools for treating lysosome-related diseases.

Looking ahead, the interdisciplinary research on lysosome damage repair mechanisms shows a robust development trend. As technology advances and research deepens, the application prospects of lysosome-targeted substances in disease treatment and regenerative medicine are expected to broaden significantly. Through collaborative efforts across disciplines, we anticipate a more comprehensive understanding of lysosome damage repair mechanisms, the development of more effective treatment methods and tools, and ultimately, greater contributions to human health.

In conclusion, lysosomes are emerging as central regulators in both health and disease. By bridging fundamental biological research with translational medicine, lysosome-targeted strategies hold great promise in providing effective treatments for a wide range of diseases. As research continues to unravel the complexities of lysosomal function and repair, new horizons in disease treatment and regenerative medicine will undoubtedly emerge.

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Author contributions
JB and YC collected, analyzed, and interpreted data and wrote the manuscript, GH and NW designed and developed the methodology, and the principal supervisor and funder of the study. MG and XS reviewed the review and make some suggestions for the manuscript. JS and RJJ help review for the revision manuscript for reviewer comments.

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Data availability
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Declarations

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