Journal of Cellular Physiology

WILEY

Journal of Cellular Physiology

REVIEW ARTICLE OPEN ACCESS

Lysosomal Repair in Health and Disease

Jinrui Xun[1] | Jay Xiaojun Tan[1,2]

[1]Aging Institute, University of Pittsburgh School of Medicine/University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA | [2]Department of Cell Biology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Correspondence: Jay Xiaojun Tan (Jay.Tan@pitt.edu)

Received: 15 March 2025 | **Revised:** 17 April 2025 | **Accepted:** 21 April 2025

Funding: J.X.T. acknowledges a grant from the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH) under the award numbers R35GM150506.

Keywords: annexins | Atg8ylation | CASM | ESCRT | lysosomal membrane permeabilization | Lysosomal repair | microlysophagy | PITT | stress granules

ABSTRACT

Lysosomes are essential organelles degrading a wide range of substrates, maintaining cellular homeostasis, and regulating cell growth through nutrient and metabolic signaling. A key vulnerability of lysosomes is their membrane permeabilization (LMP), a process tightly linked to diseases including aging, neurodegeneration, lysosomal storage disorders, and cardiovascular disease. Research progress in the past few years has greatly improved our understanding of lysosomal repair mechanisms. Upon LMP, cells activate multiple membrane remodeling processes to restore lysosomal integrity, such as membrane invagination, tubulation, lipid patching, and membrane stabilization. These repair pathways are critical in preserving cellular stress tolerance and preventing deleterious inflammation and cell death triggered by lysosomal damage. This review focuses on the expanding mechanistic insights of lysosomal repair, highlighting its crucial role in maintaining cellular health and the implications for disease pathogenesis and therapeutic strategies.

1 | Introduction

Tires serve as a cushion that absorbs the shocks and impacts from the road to safeguard the vehicle for a smooth ride. However, even the most durable tires are prone to damage. At some point, everyone experiences a flat or punctured tire. If addressed promptly, the damage can be repaired, allowing the vehicle to continue its journey. However, if left unchecked, even minor damages can develop into significant issues that compromise the vehicle's safety. In severe cases, the tire must be replaced to maintain the vehicle's functionality. Similarly, in our cells, lysosomes function as the "tires" which clear cellular stress to maintain homeostasis and cell function. Like tires, lysosomes are vulnerable to damage and are often promptly repaired, the failure of which can result in serious consequences, such as senescence or cell death.

Lysosomes are degradative organelles with acidic luminal pH and dozens of hydrolytic enzymes. They are the center for cellular detection of nutrients and metabolic signals in control of cell growth, which is often targeted for healthy aging or longevity promotion (Tan and Finkel 2023). Lysosomes degrade a wide range of substrates delivered through macroautophagy, microautophagy, or endocytosis. Lysosomal substrates range from regular macromolecules, to hyperactivated signaling complexes, to misfolded proteins, to damaged organelles, to extracellular cargos and invading pathogens. Lysosomes coordinate with many other organelles and cellular components in handling substrates destined for hydrolytic breakdown. In response to various types of cellular stress, the entire lysosomal substrate degradation system—including autophagic substrate delivery, and lysosomal quantity, quality, acidification, and activity—is often upregulated to enhance cellular stress clearance (Tan and Finkel 2023). Given that the scale of this system can be adjusted based on cellular stress status, we refer to this lysosomal degradation network as the Lysosomal Processing and Adaptation System (LYPAS) (Tan and Finkel 2023). LYPAS

incorporates not only lysosomes, but also lysosomal substrate delivery pathways, enzyme trafficking systems, acidification, nutrient recycling, osmoregulation, lysosomal biogenesis, and lysosomal quality control (Tan and Finkel 2023).

As a general cellular stress clearance system, LYPAS is frequently compromised in pathological conditions, diminishing cellular stress tolerance, causing inflammation and cell death. This is particularly relevant in aging and diseases, where the demand for LYPAS activity rises to cope with elevated cellular stress and damage. One emerging defect of LYPAS is impaired integrity of lysosomes themselves. Endolysosomal (referred to as lysosomal hereafter) membrane damage or permeabilization (LMP), is frequently found in both normal physiology and disease pathogenesis (Wang et al. 2018). A wide range of pathologies are associated with LMP, such as normal aging, Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis (ALS), lysosomal storage disorders (LSDs), atherosclerosis, autoimmune diseases, inflammatory diseases, and ischemia-reperfusion injury (Tan and Finkel 2023; Wang et al. 2018; Meyer and Kravic 2024; Gros and Muller 2023). The common occurrence of LMP across diverse diseases underscores the vulnerability of lysosomal membranes to damage. They are vulnerable to reactive oxygen species (ROS), microbes, nanoparticles, pathogenic protein aggregates, lysosomotropic compounds, and other cellular stressors (Serrano-Puebla and Boya 2018; Gómez-Sintes et al. 2016). Cells must maintain the integrity of lysosomal membranes for cellular homeostasis. In healthy cells, efficient repair mechanisms rapidly restore lysosomal integrity, preventing cell death and maintaining metabolic balance. When the repair fails, damaged lysosomes can release toxic enzymes, triggering inflammation, autophagy dysfunction, and cell death (Gómez-Sintes et al. 2016), highlighting the importance of lysosomal membrane repair in maintaining cellular health and preventing disease pathogenesis.

In the past few years, our understanding of lysosomal repair mechanisms has rapidly expanded. Following LMP, various protein complexes are activated to facilitate lysosomal membrane stabilization and repair, involving robust membrane remodeling such as invagination, tubulation, lipid patching, and protein-mediated membrane stabilization (Figure 1). Thus, our cells are resourceful in directly repairing damaged lysosomes, which will be the focus of this review. When repair efforts fail, "lysophagy," the degradation of lysosomes by macroautophagy, is activated to restrict harmful effects of lysosomal damage, which have been recently reviewed (Meyer and Kravic 2024; Yang and Tan 2023; Henn et al. 2025; Jia et al. 2025). Another critical part of lysosomal quality control is the regeneration of proto-lysosomes from damaged ones as well as de novo lysosomal biogenesis driven by transcription factor EB (TFEB)/TFE3, which further improves cellular stress resistance (Meyer and Kravic 2024; Yang and Tan 2023; Henn et al. 2025; Jia et al. 2025; Martina 2014). In this review, we focus on the recent progress in the mechanistic understanding of direct lysosomal repair and discuss their implications for health and disease.

2 | Membrane Invagination: Selective Repair via Microlysophagy

A common mechanism to repair damaged lysosomal membranes is to seal membrane pores by pushing it away from the cytosol. Endosomal sorting complex required for transport (ESCRT) is the first machinery known to directly repair damaged lysosomes (Radulovic et al. 2018; Skowyra et al. 2018). The most well-known function of ESCRT is intraluminal sorting, during which the limiting membrane of endolysosomes is pushed away from the cytosol to form intraluminal vesicles (ILVs) (Olmos 2022; Vietri et al. 2020a). This process is also referred to as microautophagy or microlysophagy. The same mechanism is thought to also act on the damage sites of lysosomes for rapid membrane repair (Figure 2).

2.1 | ESCRT-Mediated Repair

The ESCRT machineries are among the best characterized membrane-remodeling protein complexes. They maintain the integrity of multiple subcellular membranes including the plasma membrane, the nuclear envelop, autophagosomes, and lysosomes (Olmos 2022; Vietri et al. 2020b). The ESCRT pathway consists of a series of protein complexes (ESCRT-0, -I, -II, and -III) that work together to recognize, sequester, and repair the damaged portions of a target membrane (Olmos 2022; Vietri et al. 2020b).

ESCRT is a fast-acting complex recruited to lysosomes immediately upon LMP, typically within a few minutes (Radulovic et al. 2018; Skowyra et al. 2018; Tan and Finkel 2022). The

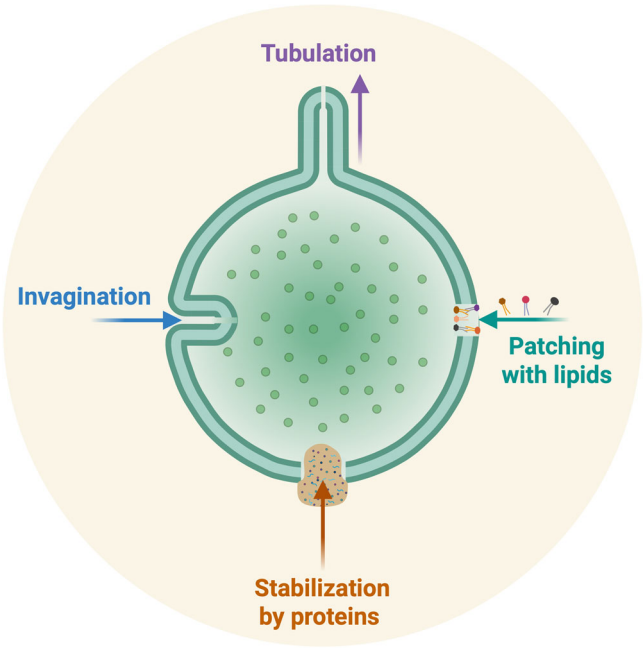

FIGURE 1 | Overview of cellular strategies in lysosomal repair. In theory, lysosomal membrane damage can be repaired through at least four distinct strategies: (1) invagination of the damaged membrane segment into the lysosomal lumen for degradation, also known as microlysophagy; (2) tubulation and budding of damaged membrane segments for removal; (3) patching of damaged membranes with lipids; (4) stabilization of damaged membranes by protein assemblies, which may facilitate membrane recovery. Reports in the literature support the existence of lysosomal repair mechanisms corresponding to each of these categories, although some of these mechanisms require more in-depth investigation.

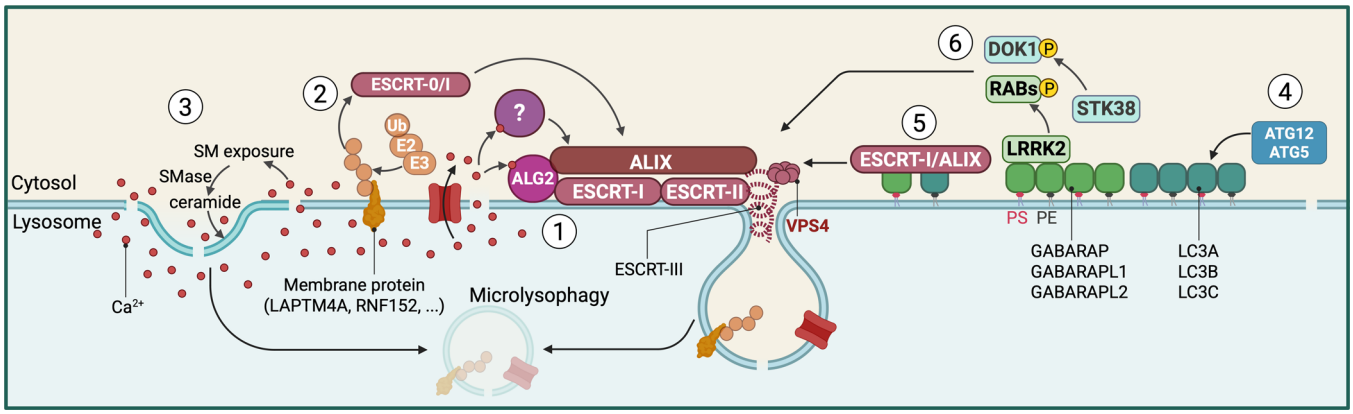

FIGURE 2 | Lysosomal repair by ESCRT-mediated membrane invagination or microlysophagy. (1) Ca^{2+} leakage from damaged lysosomes triggers ESCRT recruitment through the Ca^{2+} effector ALG2. (2) There are also ALG2-independent mechanisms for ESCRT recruitment to damaged lysosomes. Lysosomal protein ubiquitination may be one such mechanism, which recruits ESCRT-0 or -I subunits through their ubiquitin-binding motifs. Once assembled, ESCRT-III forms oligomers that seal damaged lysosomal membranes through membrane remodeling or intraluminal membrane invagination (microlysophagy). (3) ESCRT-independent membrane invagination has also been proposed through Ca^{2+}-dependent sphingomyelin (SM) exposure and subsequent SM conversion to ceramide. (4) CASM/lysosomal membrane Atg8ylation through the ATG5-ATG12 E3-like complex also plays a role in ESCRT recruitment. It is yet to be determined if ALG2 recruits ESCRT independently of CASM. (5) The lipid conjugation of ATG8 proteins, particularly GABARAPs, is critical for ALIX recruitment in response to lysosomal membrane damage. (6) The ESCRT recruitment and function are further regulated by STK38 and LRRK2. LAPTM4A, lysosomal associated protein transmembrane 4A; RNF152, Ring Finger Protein 152; ALG2, apoptosis-linked gene 2; ALIX, ALG2-interacting protein X; VPS4, vacuolar protein sorting 4; STK38, serine/threonine-protein kinase 38; DOK1, docking protein 1; PS, phosphatidylserine; PE, phosphatidylethanolamine.

recruitment of ESCRTs likely initiates with lysosomal Ca^{2+} release (Figure 2), as lysosomes are Ca^{2+} stores with their luminal Ca^{2+} level comparable to that inside the ER (Li et al. 2019). The Ca^{2+}-binding protein programmed cell death protein 6 (PDCD6)/apoptosis linked gene 2 (ALG2) plays a key role in Ca^{2+}-dependent ESCRT recruitment in plasma membrane repair (Scheffer et al. 2014), and it also appears to initiate ESCRT assembly on damaged lysosomes. Indeed, ALG2 can be recruited by either lysosomal damage (Skowyra et al. 2018; Shukla et al. 2022) or LMP-independent lysosomal Ca^{2+} release, through both electrostatic and hydrophobic interactions (Shukla et al. 2024; Li et al. 2016). Ca^{2+}-binding is sufficient to trigger the membrane recruitment of ALG2, which in turn further recruits ESCRT-III subunits through either ALG2-interacting protein X (ALIX) or ESCRT-I/II (Shukla et al. 2022). This mechanism is strongly supported by in vitro reconstitution of ALG2-mediated ESCRT assembly and by the colocalization of ALG2 with ESCRT subunits on damaged lysosomes in cells (Shukla et al. 2022). The ESCRT-III proteins, once recruited, are expected to assemble into spirals or dome-like structures around the damage sites, leading to membrane constriction and/or intraluminal membrane scission by AAA+ ATPase VPS4 (Olmos 2022; Vietri et al. 2020a; Shukla et al. 2022). This process is energy-dependent and tightly regulated to ensure efficient membrane repair. Serine–threonine kinase 38 (STK38) is recruited to damaged lysosomes where it promotes ESCRT disassembly through phosphorylating a scaffold protein, docking protein 1 (DOK1), which triggers the subsequent recruitment of VPS4 for membrane scission (Ogura et al. 2023).

The ALG2-ESCRT system not only rapidly repairs damaged lysosomes, but it also protects lysosomes from potential osmotic rupture (Chen et al. 2024). Specifically, ALG2 is recruited to intact lysosomes by Ca^{2+} signaling due to either lysosomal osmotic stress or activation of TRPML1, a lysosomal Ca^{2+} channel (Chen et al. 2024). In this context, ALG2 is critical for lysosomal resistance to potential osmotic rupture, in a way dependent on ALG2-mediated ESCRT recruitment (Chen et al. 2024). However, when lysosomes are damaged, knockdown of ALG2 did not affect lysosomal recruitment of CHMP4B, an ESCRT-III subunit (Yim et al. 2022), suggesting additional ALG2-independent lysosomal ESCRT recruitment. Since the double knockdown of ALIX and tumor susceptibility gene 101 (TSG101), an ESCRT-I subunit, fully abolishes ESCRT-III recruitment to damaged lysosomes (Skowyra et al. 2018), the ALG2-independent mechanism for ESCRT-III recruitment should act upstream of ALIX or TSG101.

Although ESCRT-mediated membrane constriction might be sufficient to directly seal lysosomal pores, such repair may also involve the turnover of lysosomal membrane components or microlysophagy if membranes around the pore are sorted into the lysosomal lumen as ILVs. Microlysophagy is observed in response to lysosomal osmotic stress or glucose starvation, which is dependent on autophagy protein 5 (ATG5), a key component of the ATG8-conjugation system, but independent of macroautophagy (Lee et al. 2020). Such macroautophagy-independent conjugation of ATG8 (LC3s or GABARAPs in mammalian cells) to the membrane has been referred to as noncanonical membrane Atg8ylation (Deretic et al. 2024; Kumar et al. 2021), noncanonical LC3 or GABARAP lipidation (Florey et al. 2015), noncanonical autophagy (Deretic et al. 2024; Durgan and Florey 2022), or conjugation of ATG8 to single membranes (CASM) (Durgan and Florey 2022), among other names, but CASM has been most widely used in literature. The role of CASM in ESCRT-mediated microlysophagy is supported by the regulation of ESCRT assembly through lysosomal GABARAP lipidation (Ogura et al. 2023). Indeed, GABARAPs associate with VPS37A, an ESCRT-I subunit, and ALIX on damaged lysosomes (Ogura et al. 2023; Corkery 2024;

Javed et al. 2023). Thus, CASM-dependent lysosomal ESCRT recruitment may be redundant with ALG2-dependent ESCRT assembly (Figure 2).

A highly conserved ubiquitination-driven, ESCRT-mediated microlysophagy pathway may also contribute to lysosomal repair (Zhu et al. 2017; Zhang et al. 2021). This pathway is initiated by the ubiquitination of specific lysosomal membrane proteins, which recruits ESCRT complexes for membrane inward budding (Li et al. 2015a, 2015b) (Figure 2). Such protein ubiquitination and subsequent turnover by microlysophagy have been observed constitutively for certain substrates such as lysosomal-associated transmembrane protein 4 A (LAPTM4A) and RNF152, a transmembrane E3 ubiquitin ligase (Zhang et al. 2021). Selective turnover of other lysosomal membrane proteins has been observed during starvation or lysosomal stress responses (Lee et al. 2020; Li et al. 2015a, 2015b; Arines et al. 2021). Since lysosomal membrane damage involves extensive protein ubiquitination (Hung et al. 2013; Maejima et al. 2013; Gahlot et al. 2024; Teranishi et al. 2022; Kravić et al. 2022; Koerver et al. 2019; Chauhan et al. 2016), such ubiquitination might drive ESCRT-mediated microlysophagy. For example, transmembrane protein 55B (TMEM55B)-dependent ubiquitination facilitates the recruitment of ubiquitin-binding ESCRT subunits for lysosomal repair during oxidative stress (Jeong et al. 2024). The ubiquitination-driven intraluminal sorting may function in parallel with, or be an integral part of, CASM-dependent microlysophagy.

Thus, the ESCRT complexes provide a rapid repair mechanism that is expected to quickly fix small pores on the lysosomal membrane. The assembly of ESCRT on damaged lysosomes appears to be driven by both ALG2-dependent and -independent mechanisms. The latter might involve additional Ca^{2+} effectors, ATG8 proteins, direct ESCRT recruitment by ubiquitin, or effectors of membrane curvature at the damage site. The potential redundancy in ESCRT recruitment ensures efficient lysosomal engagement of this complex for rapid repair.

2.2 | Sphingomyelin-Mediated Inward Invagination

The luminal budding of damaged lysosomal membranes has also been proposed to occur through ESCRT-independent mechanisms involving sphingolipids (Ellison et al. 2020; Niekamp et al. 2022) (Figure 2). Sphingomyelin, an abundant sphingolipid normally restricted to the luminal leaflet of the lysosomal membrane, is exposed on the cytosolic side during lysosomal damage (Ellison et al. 2020; Niekamp et al. 2022). Such redistribution is achieved by $Ca2^{+}$-dependent lipid scrambling, followed by metabolic conversion of sphingomyelin to ceramide by neutral sphingomyelinases (Niekamp et al. 2022). Due to its cone-like molecular shape, ceramide on the cytosolic leaflet of endosomal membranes can generate negative membrane curvature for intraluminal membrane budding (Trajkovic et al. 2008). Similarly, ceramide accumulation on the lysosomal surface is thought to induce a negative curvature, allowing microlysophagy-like membrane budding in the absence of ESCRT (Niekamp et al. 2022). It seems likely that ESCRT and ceramide may work together for optimal membrane repair efficiency.

Interestingly, sphingomyelin-to-ceramide conversion by acid sphingomyelinase (ASM) on the luminal side of the lysosomal membrane also promotes lysosomal integrity (Kirkegaard et al. 2010). Consistently, loss of function of the ASM gene, which causes sphingomyelin accumulation in Niemann Pick disease type A (NPA) (Brady et al. 1966), is accompanied by increased lysosomal leakage (Gabandé-Rodríguez et al. 2014). The membrane stabilization activity from ceramide located to either leaflet of the lysosomal membrane may involve distinct mechanisms. New insights may come from communications of ceramide or sphingomyelin with the other lysosomal membrane remodeling mechanisms.

3 | Membrane Tubulation: Shedding and Recycling

In contrast to membrane invagination, lysosomes may be repaired alternatively through membrane tubulation. In theory, the budding and shedding of damaged membranes could directly repair lysosomes; otherwise, new proto-lysosomes may be formed from severely damaged lysosomes through the budding of intact membranes, leaving the irreparable part for lysophagy. A classic example of lysosomal membrane budding is autophagic lysosome reformation (ALR) (Yu 2010a). In response to prolonged starvation, ALR generates nascent lysosomes by pulling tubular membrane structures from autolysosomes, which are then severed to form proto-lysosomes that gradually mature (Yu 2010a). Since lysosomal tubulation can be triggered by Ca^{2+} release through the lysosomal cation channel TRPML1 (Li et al. 2016), it would also be induced by Ca^{2+} leakage during LMP. Consistently, several lines of evidence have shown lysosomal tubulation in response to LMP, although it is less understood whether the bud-off membranes are damaged or not.

One example of LMP-induced lysosomal tubulation is driven by leucine-rich repeat kinase 2 (LRRK2) (Bonet-Ponce et al. 2020), a risk gene commonly mutated with increased activity in Parkinson's disease (Rocha et al. 2022; Bentley-DeSousa et al. 2025a) (Figure 3). In response to LMP, LRRK2 is recruited to lysosomes by CASM (Eguchi et al. 2024). Lysosomal LRRK2 phosphorylates multiple Ras-related in brain (RAB) GTPases to recover lysosomal function (Bonet-Ponce et al. 2020; Eguchi et al. 2018; Herbst et al. 2020). The phosphorylation of RAB10 and RAB35 by LRRK2 further triggers lysosomal recruitment of a motor adapter protein c-Jun N-terminal kinase (JNK)–interacting protein 4 (JIP4) (Bonet-Ponce et al. 2020). JIP4 in turn mediates the formation of lysosomal-associated membrane protein 1 (LAMP1)-negative tubular structures and subsequent vesicle shedding from damaged lysosomes (Bonet-Ponce et al. 2020). This LMP-induced, JIP4-mediated lysosomal tubulation is dependent on LRRK2 and termed lysosomal tubulation/sorting driven by LRRK2 (LYTL) (Bonet-Ponce et al. 2020). Since LMP-induced LRRK2 recruitment is mediated by CASM (Eguchi et al. 2024) and specifically GABARAP lipidation (Bentley-DeSousa et al. 2025b), LYTL should also be CASM-dependent.

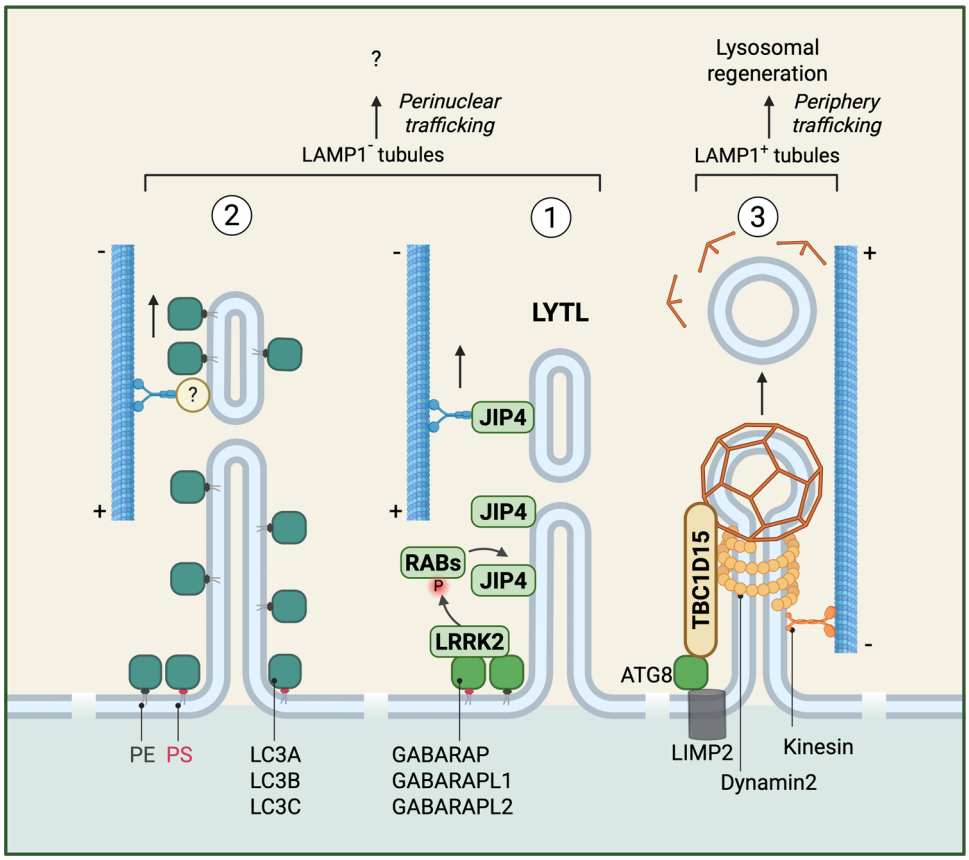

FIGURE 3 | LMP-induced lysosomal membrane tubulation. Lysosomal membrane damage triggers the tubulation of both LAMP1-positive and -negative membranes. (1) CASM/lysosomal membrane Atg8ylation plays a key role in recruiting LRRK2 to damaged lysosomes, which in turn triggers JIP4-mediated lysosomal tubulation, known as lysosomal tubulation/sorting driven by LRRK2 (LYTL). (2) CASM also associates with LRRK2-independent tubulation of LC3-positive, LAMP1-negative lysosomal membranes. The exact function of these CASM-related lysosomal tubulation is yet to be determined. (3) Another lysosomal tubulation pathway is mediated by the RAB7 GTPase-activating protein TBC1D15 and contributes to lysosomal reformation. In response to severe lysosomal damage, macroautophagy-related ATG8 recruits TBC1D15 to the lysosome independent of CASM. TBC1D15 then recruits multiple proteins from the autophagic lysosomal reformation pathway, including clathrin and dynamin2. TBC1D15-dependent lysosomal tubulation recycles lysosomal components before autophagic turnover of overly damaged lysosomes. JIP4, c-Jun N-terminal kinase (JNK)–interacting protein 4; PS, phosphatidylserine; PE, phosphatidylethanolamine; LRRK2, leucine-rich repeat kinase 2. LAMP1, lysosomal-associated membrane protein 1.

LMP-induced CASM is additionally connected with lysosomal tubulation seemingly independent of LRRK2 (Cross et al. 2023) (Figure 3). These tubules are LAMP1-negative but LC3-positive and are not affected when LRRK2 is inhibited (Cross et al. 2023). Although the exact roles of LYTL and LMP-induced LC3 tubules in lysosomal damage response are still under investigation, they might have significant impact on lysosomal quality control and Parkinson's disease. Of note, a pathogenic LRRK2 mutant implicated in Parkinson's disease showed increased lysosomal localization, JIP recruitment, and lysosomal tubulation (Bonet-Ponce et al. 2020).

Membrane tubules can also be regenerated from damaged lysosomes for proto-lysosome formation (Bhattacharya et al. 2023; Eriksson et al. 2020) (Figure 3). In the late stages of lysosomal damage by LLOME, a RAB7 GTPase-activating protein (GAP) TBC1D15 is recruited to the lysosome by binding to ATG8 (Bhattacharya et al. 2023). TBC1D15 connects damaged lysosomes with membrane budding and tubulation proteins, such as clathrin and kinesin family member 5b (KIF5B), followed by membrane scission by dynamin-2 (Bhattacharya et al. 2023). This process mediates lysosomal regeneration independently of TFEB-dependent transcriptional lysosomal biogenesis (Bhattacharya et al. 2023). TBC1D15-dependent lysosomal tubules are LAMP1-positive, consistent with their roles in lysosomal regeneration (Bhattacharya et al. 2023). This regeneration process is critical for the turnover of galectin 3, a cytosolic lectin that binds to exposed β-galactoside on damaged lysosomes, after LLOME washout in a macroautophagy-dependent manner (Bhattacharya et al. 2023). It seems likely that part of the lysosomal components is recycled for lysosomal reformation before the remaining is destroyed by lysophagy.

In summary, LMP triggers multiple tubulation processes on the lysosome, underscoring the dynamic nature of lysosomal repair or regeneration. Future studies are needed to clarify the functions and regulation of each tubulation pathway. LRRK2-dependent and -independent lysosomal tubules, including JIP4-positive and LC3-positive tubules, may represent cellular responses to different stages of lysosomal membrane damage, as LRRK2 appears to be recruited at a later stage (Wang et al. 2025). Such lysosomal membrane dynamics could be

disrupted by LRRK2 mutations in Parkinson's disease. Lysosomal regeneration mechanisms, such as those involving TBC1D15 and macroautophagy, further demonstrate cellular capacity to restore lysosomal integrity following damage.

4 | Lipid Patching: Rapid Repair Through Lipid Delivery

While membrane invagination and tubulation are effective strategies to repair damaged membranes, a more direct repair approach is lipid patching—filling membrane pores through lipid delivery. Two biochemical screens investigating lysosomal changes upon LMP, using proteomics and lipidomics respectively, reached the same conclusion that endoplasmic reticulum (ER)-to-lysosome lipid transfer mediates rapid lysosomal repair (Tan and Finkel 2022; Radulovic et al. 2022). This repair mechanism is driven by LMP-induced lysosomal phosphatidylinositol 4-phosphate (PI4P) signaling and is thus designated the phosphoinositide-initiated membrane tethering and lipid transport (PITT) pathway (Tan and Finkel 2022).

LMP triggers rapid membrane contacts between the ER and damaged lysosomes through PI4P signaling (Figure 4). Phosphatidylinositol 4-kinase 2-alpha (PI4K2A), recruited upon lysosomal Ca^{2+} leakage, directly generates PI4P on damaged lysosomes by phosphorylating phosphatidylinositol (PI) (Tan and Finkel 2022; Radulovic et al. 2022). PI4P further recruits multiple PI4P effectors from the oxysterol-binding protein (OSBP)-related protein (ORP) family. Five ORP family members are redundantly recruited, including ORP9, ORP10, ORP11, OSBP, and ORP1L (Tan and Finkel 2022; Radulovic et al. 2022; Anand et al. 2023). They tether damaged lysosomes to the ER by simultaneously binding to PI4P on the lysosome and vesicle-associated membrane protein-associated protein A (VAPA) and VAPB on the ER (Tan and Finkel 2022; Radulovic et al. 2022).

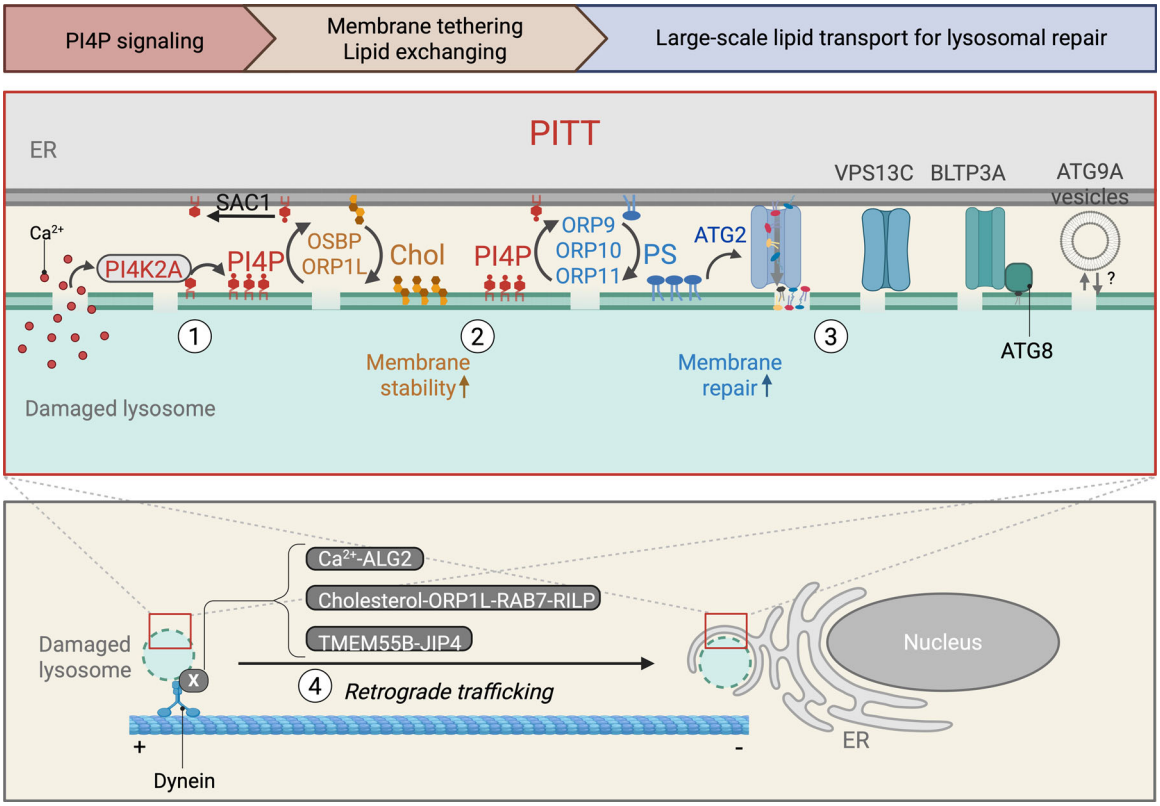

FIGURE 4 | The PITT pathway – patching damaged lysosomes through lipid transfer. The phosphoinositide-initiated membrane tethering and lipid transport (PITT) pathway mediates rapid lysosomal repair through ER-to-lysosome lipid transfer. (1) PI4P signaling: Ca^{2+} leakage from damaged lysosomes triggers lysosomal recruitment of PI4K2A which generates prominent levels of phosphatidylinositol-4-phosphate (PI4P) on the lysosomal membrane as a signaling messenger. (2) Membrane tethering and lipid exchanging: PI4P serves as a damage signal to recruit oxysterol-binding protein (OSBP) and OSBP-related proteins (ORP9/10/11) which tether damaged lysosomes to the ER membrane via simultaneous interactions with the lysosomal PI4P and ER-anchored adapter proteins vesicle-associated membrane protein (VAMP)-associated protein A and B (VAPA/VAPB); at the membrane contacts, OSBP and ORPs mediate PI4P/cholesterol and PI4P/phosphatidylserine (PS) exchanging between ER and lysosomes, leading to lysosomal accumulation of both cholesterol and PS. Increased cholesterol levels improve lysosomal membrane rigidity and stability. (3) Lysosomal repair via large-scale lipid transfer: lysosomal PS activates ATG2-mediated lipid delivery to repair damaged membranes. Additional bridge-like lipid transfer proteins such as VPS13C and BLTP3A are also recruited to damaged lysosomes. The lipid scramblase ATG9 may also regulate lysosomal membrane remodeling. (4) Damaged lysosomes undergo retrograde transport to the ER-extensive perinuclear region, which may facilitate lysosome-ER membrane contact formation. Multiple mechanisms promote lysosomal retrograde trafficking upon membrane damage. Chol, cholesterol; PS, phosphatidylserine; SAC1, ER-anchored PI4P phosphatase; RILP, Rab-interacting lysosomal protein; JIP4, c-Jun-amino-terminal kinase-interacting protein 4; ER, endoplasmic reticulum; ALG2, apoptosis-linked gene 2; BLTP3A, bridge-like lipid transfer protein family member 3A.

At the ER-lysosome contact sites, multiple lipid transfer events contribute to rapid lysosomal repair (Figure 4). The ORP family proteins are established lipid exchangers at membrane contact sites (Delfosse et al. 2020; Mesmin et al. 2013). The five ORPs fall into two groups: ORP9, ORP10, and ORP11 form heterodimers mediating ER-to-lysosome transfer of phosphatidylserine (PS) in exchange for lysosomal PI4P (Tan and Finkel 2022), whereas OSBP and ORP1L each seems sufficient to mediate PI4P-diven, ER-to-lysosome transfer of cholesterol (Tan and Finkel 2022; Radulovic et al. 2022). Thus, LMP-induced PI4P signaling drives ER-to-lysosomal transfer of both PS and cholesterol. Interestingly, either PS or cholesterol is sufficient to support rapid lysosomal repair (Tan and Finkel 2022). Cholesterol can increase membrane rigidity and thus provide resistance to lysosomal membrane damage (Radulovic et al. 2022; Appelqvist et al. 2012; Gutierrez et al. 2016). Meanwhile, PS further activates another large-scale lipid transfer protein ATG2 for the direct lipid patching of lysosomal pores, independent of the established roles of ATG2 in macroautophagy (Tan and Finkel 2022). ATG2 belongs to the bridge-like lipid transfer protein (BLTP) family (Neuman et al. 2022) and carries a long hydrophobic groove which is proposed to mediate bulk, non-selective lipid transfer between membranes (Osawa et al. 2020, 2019; Maeda et al. 2019). The amphipathic C-tail of ATG2 appears to recognize PS-positive lysosomal membrane pores to precisely direct lipid unloading (Tan and Finkel 2022).

While ATG2 is proposed to work with lipid scramblases on both the ER and the expanding phagophore during macroautophagy (Li et al. 2021; Huang et al. 2021; Ghanbarpour et al. 2021; Matoba et al. 2020), it is still unclear if a lipid scramblase is involved in rapid lysosomal repair. Since the two leaflets of the lysosomal membrane are interconnected at the damage site, it was speculated that a lysosomal lipid scramblase may not be necessary (Yang and Tan 2023). However, ATG9A, a lipid scramblase working with ATG2 in autophagosome biogenesis, seems to be dynamically localized to lysosomes upon LMP (De Tito 2024; Peng et al. 2025) (Figure 4), suggesting that ATG9A might provide a potential membrane source or lipid scrambling activity during lysosomal repair. Interestingly, both ATG9A and ATG2 are also implicated in plasma membrane repair (Claude-Taupin et al. 2021). Thus, it would be interesting to further investigate the roles of ATG9A and the lipid unloading mechanisms for ATG2 on the lysosome.

In addition to ATG2, another two BLTPs, VPS13C and BLTP3A (UHRF1BP1), have been recently proposed to regulate lysosomal repair (Wang et al. 2025; Hanna 2024) (Figure 4). Similarly to ATG2, VPS13C is rapidly recruited to damaged lysosomes upon LMP (Wang et al. 2025). Different from ATG2 and VPS13C, BLTP3A associates with and clusters small vesicles to lysosomes in resting conditions through an interaction with RAB7 (Hanna 2024). Interestingly, upon lysosomal damage, the original interactions are lost and quickly replaced with lysosomal re-association of BLTP3A through its LC3-interacting region (LIR) in a CASM-dependent manner (Hanna 2024). By contrast, both ATG2 and VPS13C are recruited to damaged lysosomes independently of CASM (Tan and Finkel 2022; Wang et al. 2025), potentially by directly sensing lysosomal membrane packing defects at damage sites through their C-terminal amphipathic helices (Tan and Finkel 2022; Wang et al. 2025). The LMP-induced recruitment of VPS13C and BLTP3A strongly suggests their potential roles in lipid transfer between the ER and lysosomes. However, it is yet to be determined whether BLTP3A and VPS13C contribute to lysosomal repair and if so, whether it is mediated by lipid transfer. Any redundancy or cooperation between ATG2 and other BLTPs in lysosomal repair should be investigated.

Since the ER-to-lysosome lipid transfer is crucial for rapid lysosomal repair, it seems important to move damaged lysosomes to the perinuclear region, where ER membranes are denser than in the peripheral area (Puhka et al. 2007). Perinuclear lysosomes are also more stationary, allowing extensive ER-lysosome contacts (Rayens et al. 2022). We hypothesize that damaged lysosomes may be transported to the perinuclear area by multiple redundant mechanisms (Figure 4). First, Ca^{2+} leakage from the lysosome may promote the perinuclear trafficking of lysosomes through ALG2, a Ca^{2+}-binding protein, and dynein motors (Li et al. 2016; Vergarajauregui et al. 2009). Second, cholesterol accumulation in lysosomes through the PITT pathway likely further strengthens their perinuclear localization, similarly to lysosomal storage diseases (Shen et al. 2012; Chen et al. 2008). Specifically, the cholesterol–Rab7–RILP axis is known to promote retrograde lysosomal transport (Cabukusta and Neefjes 2018). Third, TMEM55B is transcriptionally upregulated by TFEB/TFE3 to promote JIP4- and dynein-dependent perinuclear transport of lysosomes (Willett et al. 2017). Thus, multiple mechanisms could drive the perinuclear movement of damaged lysosomes, presumably in favor of more efficient repair and remodeling.

In summary, the PITT pathway drives massive ER-lysosome lipid exchanges through membrane contacts, which resets lysosomal lipid compositions as a platform for rapid lysosomal repair through large-scale lipid delivery. BLTPs, such as ATG2, VPS13C, and BLTP3A, may coordinate in lysosomal repair. Lipid delivery by ATG2 and all other BLTPs is expected to be unidirectional in both macroautophagy and lysosomal repair. However, it is still unclear what is the driving force for such large-scale unidirectional lipid transport, but part of the answers could come from the different biophysical properties of the two membranes connected by BLTPs.

5 | Membrane Stabilization: Structural Support by Protein Assemblies

In addition to membrane repair by lipid remodeling and lipid patching, protein assemblies have been shown to stabilize damaged membranes (Figure 5). As protein condensation can rapidly respond to sudden changes in the cytosol, it is proposed that protein condensation functions as a first-aid response to stabilize lysosomal pores (Bussi et al. 2023).

5.1 | Stress Granules

Stress granules are dynamic, membrane-less cytoplasmic condensates consisting of nontranslating messenger ribonucleoproteins (mRNPs) that mediate global translation arrest in response to various types of stimuli such as oxidative stress or

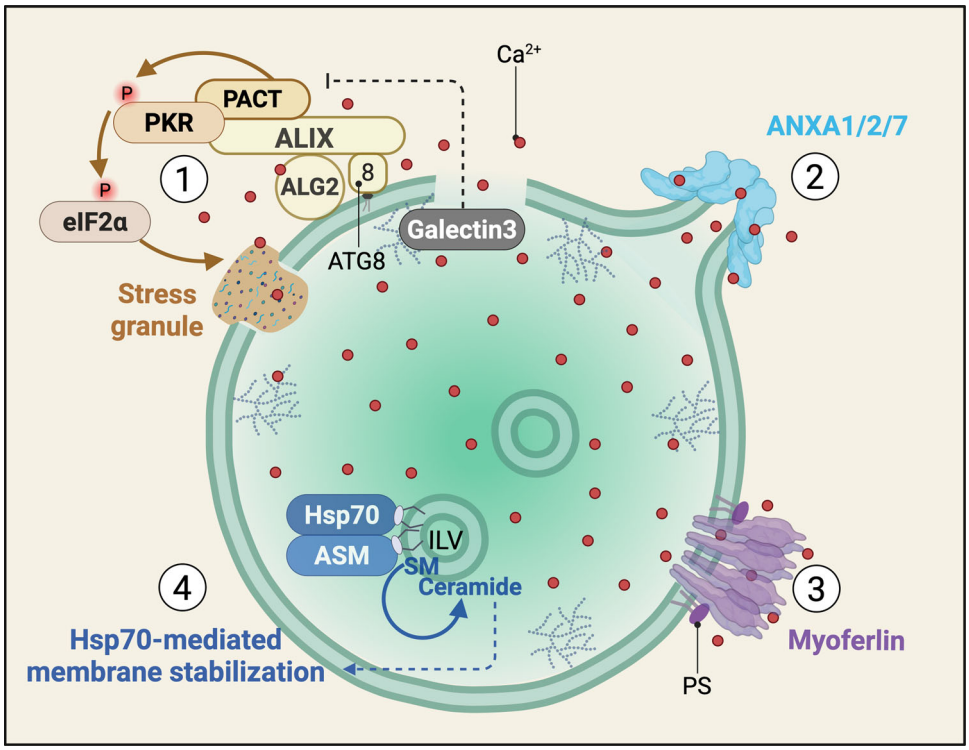

FIGURE 5 | Lysosomal membrane stabilization by multiple pathways. The lysosomal membrane is stabilized by multiple mechanisms that may contribute to lysosomal repair. (1) Stress granules are triggered both on lysosomes and in the cytosol during lysosomal membrane damage, which involves protein kinase R (PKR, EIF2AK2) phosphorylation facilitated by Ca^{2+}-dependent ALIX assembly on the lysosome. PKR subsequently phosphorylates eIF2α to activate stress granule formation. (2) Annexin A1, A2, and A7 (ANXAs) promote lysosomal repair by localizing to large membrane pores where ANXAs may oligomerize to stabilize and repair the membrane. (3) Myoferlin localization to lysosomes in cancers can increase lysosomal membrane stability, which may be driven by Ca^{2+}- and PS-stimulated Myoferlin oligomerization. (4) The heat shock chaperone protein Hsp70 promotes lysosomal membrane stability by binding to bis-(monoacylglycero)-phosphate (BMP) on intraluminal vesicles (ILVs) in the lysosomal lumen, which in turn activates acid sphingomyelinase (ASM) to convert sphingomyelin (SM) into ceramide. The latter may increase lysosomal membrane stability indirectly through improved lysosomal lipid metabolism. ALG2, apoptosis-linked gene 2; ALIX, ALG2-interacting protein X; ILV, intraluminal vesicle; PACT, protein activator of the interferon-induced protein kinase; PS, phosphatidylserine.

heat shock (Alberti et al. 2019). RNA-binding proteins G3BP1 and G3BP2 are essential components of stress granules that contribute to their formation through multivalent interactions with other molecules such as RNAs and eukaryotic translation initiation factor 2α (eIF2α) (Yang et al. 2020). In response to LMP, stress granule proteins including G3BP1 and NUFIP2 are recruited to lysosomes independently of their condensation or stress granule formation (Jia et al. 2022). Protein kinase R (PKR, also known as EIF2AK2) is activated, which in turn triggers stress granule formation likely by phosphorylating eIF2α, a key component of stress granules (Jia et al. 2022) (Figure 5). The ESCRT components ALIX and ALG2 crosstalk with stress granule formation by promoting PKR association with its activator PACT (also known as PRKRA or Protein Activator of Interferon Induced Protein Kinase EIF2AK2) (Duran et al. 2024). Interestingly, both ALIX and ALG2 are required for stress granule formation (Duran et al. 2024), although the lysosomal ALIX recruitment is dependent on CASM (Corkery 2024) whereas ALG2 directly responds to lysosomal Ca2+ leakage (Shukla et al. 2024; Chen et al. 2024). In U2OS cells, most stress granules are formed away from lysosomes (Jia et al. 2022), whereas in human induced pluripotent stem cell-derived macrophages (iPSDMs) stress granules emerge selectively on damaged lysosomes (Bussi et al. 2023). The lysosome-associated stress granules have been proposed to plug and stabilize the membrane, thus preventing potential membrane rupture and lysosomal leakage (Bussi et al. 2023).

5.2 | Annexins-Mediated Repair

Another family of proteins that repair damaged lysosomes through membrane stabilization are annexins (Figure 5). They are Ca^{2+}-dependent phospholipid-binding proteins previously reported to repair the plasma membrane (Lennon et al. 2003; Demonbreun et al. 2016; Bouter et al. 2011; Boye et al. 2017; Blackwood and Ernst 1990). Each of the ubiquitous annexins (ANXA1, A2, A4, A5, A6, A7, and A11), when stably expressed in U2OS cells, are similarly recruited to lysosomes after LMP (Yim et al. 2022; Scharf et al. 2012). Among them, ANXA1, ANXA2, and ANXA7 have been reported to mediate lysosomal repair (Yim et al. 2022; Ebstrup et al. 2023). While the ESCRT subunit CHM4A is localized to lysosomes with either small or large membrane pores, ANXA1 and ANXA2 are preferentially recruited to lysosomes with wounds larger than 4.6 nm in diameter, where annexins have a role in preventing the leakage of lysosomal contents (Yim et al. 2022). These are consistent with ESCRT-independent recruitment of annexins (Yim et al. 2022; Ebstrup et al. 2023). Of note, ANXA2 can promote the aggregation of membranes containing PS and cholesterol in

response to Ca^{2+} (ref (Blackwood and Ernst 1990); Ayala-Sanmartin et al. 2001; Drücker et al. 2014). Thus, it seems likely that the ER-to-lysosome transfer of PS and cholesterol through the PITT pathway (Tan and Finkel 2022) might contribute to annexin recruitment and subsequent membrane remodeling. This is consistent with annexin recruitment at a later time point after LMP (Yim et al. 2022), as it takes time to accumulate PS and cholesterol on the lysosome. Thus, annexin-mediated lysosomal repair might involve annexin oligomerization, membrane remodeling, and subsequent membrane sealing (Lennon et al. 2003; Demonbreun et al. 2016; Bouter et al. 2011; Boye et al. 2017). It is also likely that annexins can stabilize the damaged membrane to enable more efficient repair by ESCRT or the PITT pathway.

5.3 | Myoferlin and Hsp70

Lysosomal membranes are also potently stabilized by other proteins, such as the Ferlin family and heat-shock proteins. These proteins, when highly expressed and/or enriched in lysosomes, increase lysosomal membrane stability.

The Ferlin family of membrane repair proteins, particularly Myoferlin (MYOF) and Dysferlin (DYSF), also play a crucial role in maintaining lysosomal membrane integrity (Figure 5). In pancreatic ductal adenocarcinoma, these proteins are overexpressed and/or enriched in lysosomes, which is associated with poor prognosis (Gupta et al. 2021). MYOF appears to support tumor growth or survival by promoting effective lysosomal repair or stability and potentially facilitating cancer cell adaptation to cellular stress (Gupta et al. 2021). Like ANXA2, ferlins also show Ca^{2+}-dependent binding to PS and promote membrane fusions (Davis et al. 2002; Doherty et al. 2005). Thus, MYOF might also cooperate with the PITT pathway in lysosomal repair and membrane stabilization.

Heat-shock protein 70 (Hsp70, HSPA1A, or Hsp70.1), a stress-induced chaperone protein, stabilizes the lysosomal membrane by activating acid sphingomyelinase (ASM) which converts sphingomyelin to ceramide on intraluminal vesicles (ILVs) inside lysosomes (Kirkegaard et al. 2010) (Figure 5). In the lysosomal lumen, Hsp70 binds to the negatively charged phospholipid bis-(monoacylglycero)-phosphate (BMP) on ILVs through its N-terminal nucleotide binding domain (NBD) (Calvaresi et al. 2021). This binding increases the activity of ASM and is essential for Hsp70-mediated lysosomal membrane stabilization (Kirkegaard et al. 2010; Petersen et al. 2010). Hsp70 appears to be localized to the endolysosomal lumen through stress-induced secretion followed by endocytic trafficking, which may allow nonautonomous improvement of lysosomal membrane stability in the tissue level (De Maio 2014). Of note, Hsp70 is an ATPase which hydrolyzes ATP through its NBD (Young 2010), but it is not determined whether and how such ATPase activity contributes to its lysosomal membrane stabilization.

6 | CASM: Multi-Tasking in Lysosomal Repair

CASM, the covalent conjugation of ATG8s to the lysosomal membrane, is a common lysosomal stress response (Durgan and Florey 2022) (Figure 6). CASM involves the direct recruitment of the ATG8-conjugation machinery, ATG16L1–ATG5–ATG12 (ref (Ichimura et al. 2000); Mizushima et al. 2003), by the endolysosomal V-ATPase proton pump, independent of macroautophagy (Cross et al. 2023; Xu et al. 2019; Hooper et al. 2022). In response to lysosomal membrane damage, Tectonin Beta-Propeller Repeat Containing 1 (TECPR1) can alternatively recruit the ATG12–ATG5 complex for lysosomal Atg8ylation independent of the V-ATPase-ATG16L1 axis (Kaur et al. 2023; Corkery et al. 2023; Boyle et al. 2023; Wang 2023a). Interestingly, in CASM, ATG8 is conjugated to both PE and PS (Durgan et al. 2021), different from sole PE conjugation of ATG8 in macroautophagy. The ER-to-lysosome transfer of PS driven by the PITT pathway (Tan and Finkel 2022) may facilitate ATG8-PS conjugation during lysosomal damage. The level of Atg8ylation in response to lysosomal damage is remarkable, as all the cytosolic ATG8 proteins, even if overexpressed, are almost completely conjugated to lysosomes (Cross et al. 2023). Thus, one would expect major functions of membrane Atg8ylation or CASM in endolysosomal stress response independent of macroautophagy.

CASM is emerging as a contributor to lysosomal repair. Assays using lysosomal pH sensors revealed reduced repair efficiency in cells deficient in Atg8ylation (Corkery 2024; Wang 2023b). CASM might promote lysosomal repair through multiple mechanisms (Figure 6). (i) LC3 conjugated to damaged lysosomes associates with large-scale lipid transfer proteins, such as ATG2 and BLTP3A (Cross et al. 2023; Hanna 2024). Although CASM is not necessary to recruit ATG2 to damaged lysosomes (Cross et al. 2023), the recruitment of BLTP3A is dependent on its ATG8-binding motif (Hanna 2024). Of note, Atg8ylation on phagosomes or lysosomes in other contexts also stimulate the ATG2–ATG8 interaction, suggesting that BLTP-mediated lipid transfer is likely a general mechanism to alleviate membrane stress (Cross et al. 2023). (ii) Sphingomyelin exposure was recently found to directly recruit TECPR1 for ATG16L1-independent Atg8ylation on damaged lysosomes (Kaur et al. 2023; Boyle et al. 2023), linking sphingomyelin-mediated lysosomal repair to CASM and microlysophagy. (iii) CASM is also a platform to recruit the ESCRT complexes (ALIX and VPS37A) to damaged lysosomes (Ogura et al. 2023; Corkery 2024; Javed et al. 2023). Thus, CASM seems to coordinate several lysosomal repair pathways, including PITT, sphingomyelin, and ESCRT.

CASM also cross-talks with additional processes in lysosomal remodeling and quality control (Figure 6). (i) CASM appears to be associated with microtubule-dependent lysosomal tubulation and scission upon lysosomal damage. The dynamic LC3-positive tubules were negative for the lysosomal marker LAMP1, but they emerge from LAMP1-positive lysosomes (Cross et al. 2023). LMP-driven tubulation of LC3-positive lysosomal membranes seems to be independent of ALR (Yu 2010) or lysosome tubulation/sorting driven by LRRK2 (LYTL) (Bonet-Ponce et al. 2020). (ii) CASM can recruit LRRK2 through GABARAP lipidation, which adds another layer of regulation to ESCRT assembly on damaged lysosomes (Eguchi et al. 2018; Herbst et al. 2020). CASM-mediated LRRK2 recruitment is activated not only by lysosomal damage

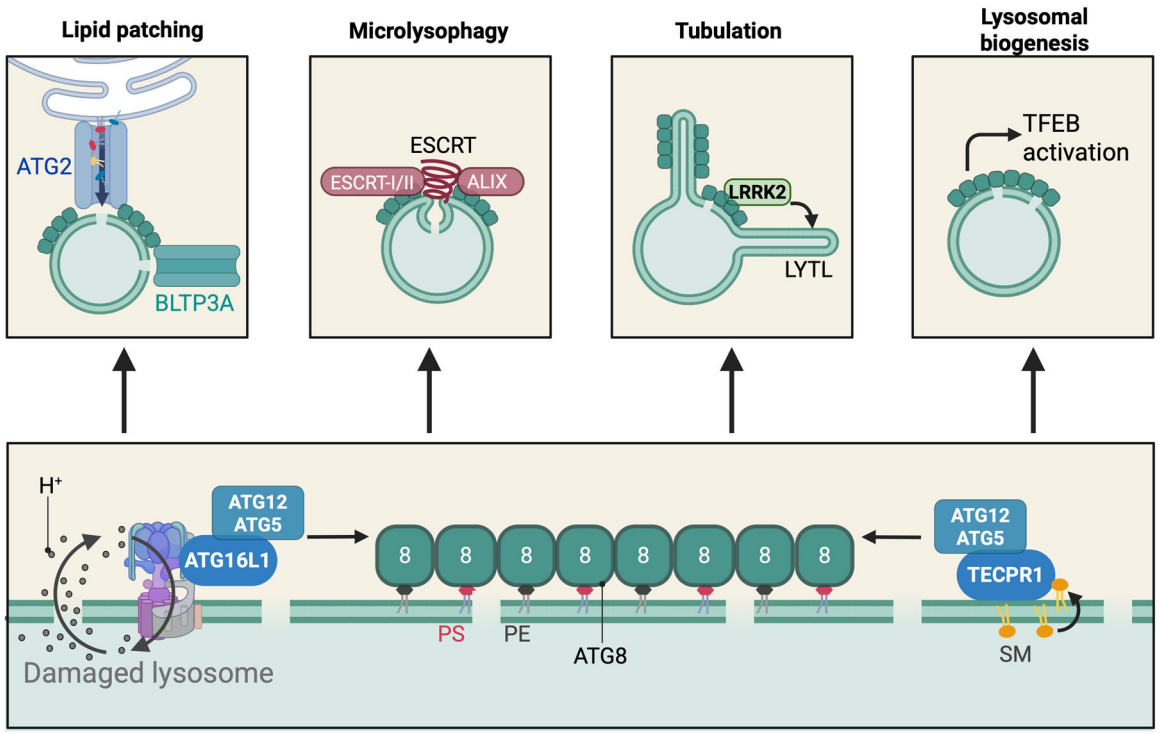

FIGURE 6 | CASM/Membrane Atg8ylation coordinates multiple lysosomal repair/quality control pathways. Conjugation of ATG8 to single membranes (CASM) or lysosomal membrane Atg8ylation is a robust response triggered by lysosomal stress including membrane damage. CASM is redundantly activated by either the V-ATPase-ATG16L1 axis or sphingomyelin (SM)-TECPR1 axis. CASM cross-talks with multiple lysosomal repair/quality control pathways through ATG8 interactions with different proteins, such as ATG2 (PITT), BLTP3A, ALIX and VPS37A (ESCRT), LRRK2 (LYTL), and FNIP/FLCN (TFEB). Most of the interactions have been clearly defined by the presence of ATG8-interacting motifs (AIM) in these proteins. BLTP3A, bridge-like lipid transfer protein family member 3A; LYTL: lysosomal tubulation/sorting driven by LRRK2; PS, phosphatidylserine; PE, phosphatidylethanolamine; TECPR1, tectonin beta-propeller repeat-containing protein 1; TFEB, transcription factor EB.

(Eguchi et al. 2024) but also during the activation of the stimulator of interferon genes (STING) (Bentley-DeSousa et al. 2025b; Huang et al. 2025), an innate immune adapter that activates CASM through its conserved proton channel activity (Xun et al. 2024; Fischer et al. 2020; Liu et al. 2023). (iii) CASM provides a robust platform to activate TFEB/TFE3 in response to diverse cellular stresses including lysosomal damage and STING activation (Nakamura et al. 2020; Kumar et al. 2020; Goodwin et al. 2021; Lv et al. 2024; Klein et al. 2024). In summary, CASM is a general lysosomal membrane stress response that communicates with lysosomal repair, recycling, and regeneration.

7 | Lysosomal Repair in Aging, Diseases and Therapies

Given the fundamental roles of lysosomes in cellular stress clearance, it is not surprising that our cells have evolved multi-layered rapid lysosomal repair mechanisms. In stressed conditions such as senescence, efficient lysosomal repair becomes particularly important, as cells rely heavily on LYPAS for stress clearance (Tan and Finkel 2023; Rovira et al. 2022). Particularly, increased lysosomal delivery of substrates, such as protein aggregates, can raise the risk of lysosomal membrane damage (Murley et al. 2025). As such, defective or insufficient lysosomal repair is associated with aging and many diseases, which should be leveraged for therapeutic potential.

Genetic defects in lysosomal repair are increasingly recognized as key contributors to neurodegenerative diseases such as Alzheimer's and Parkinson's. Loss of PI4K2A, the key enzyme of the PITT pathway, causes hereditary spastic paraplegias (HSP)-like neurodegeneration in mice with lipofuscin accumulation in Purkinje neurons, an indication of lysosomal defects (Simons et al. 2009). As intercellular spreading of prion-like pathogenic proteins involves lysosomal escape through membrane damages, disrupting PITT- or ESCRT-mediated lysosomal repair exacerbates tau fibril spreading in Alzheimer's disease models (Tan and Finkel 2022; Chen et al. 2019). Damaged lysosomes also recruit and activate LRRK2 (Bonet-Ponce et al. 2020; Eguchi et al. 2024, 2018; Herbst et al. 2020), the activity of which seems to regulate ESCRT recruitment and lysosomal tubulation (Bonet-Ponce et al. 2020; Eguchi et al. 2024, 2018; Herbst et al. 2020; Bonet-Ponce and Cookson 2022). It is likely that acute LRRK2 activation plays a beneficial role in lysosomal quality control, but chronic LRRK2 activation due to either mutations or long-term lysosomal stress may compromise lysosomal functions. Another Parkinson's disease risk gene VPS13C is also recruited to damaged lysosomes (Wang et al. 2025). Loss of function of VPS13C clearly activates TFEB-mediated lysosomal biogenesis (Hancock-Cerutti et al. 2022), a common response during cell stress including lysosomal stress (Yang and Tan 2023; Napolitano and Ballabio 2016). Loss of VPA13C also activates the cGAS–STING innate immune pathway (Hancock-Cerutti et al. 2022), the chronic activation of which is associated with normal aging and Alzheimer's and

Parkinson's diseases (Carling et al. 2024; Xie et al. 2023; Udeochu et al. 2023; Gulen et al. 2023; Sliter et al. 2018). It is important to investigate what specific roles VPS13C and other BLTPs have on damaged lysosomes and how such roles could be targeted for lysosomal benefits.

Lysosomal storage diseases are also associated with failures in lysosomal repair. Lysosomal cholesterol overload or sphingomyelin accumulation, often seen in lysosomal storage disease such as Niemann-Pick disease, type C (NPC), causes persistent LMP, abnormal PI4P signaling (Lim et al. 2019), and dysfunctional ESCRT aggregation on lysosomes, leading to broad lysosomal dysfunction (Yong et al. 2024). These observations imply lysosomal repair failure, despite the activation of PI4P signaling and ESCRT recruitment. Therefore, a different lysosomal repair or stabilization strategy is needed to restore lysosomal stability. Indeed, recombinant Hsp70 has been found to reduce lipid storage in different NPC disease models, including NPC-knockout and loss-of-function mutations (Gray et al. 2022; Pipalia et al. 2021). Remarkably, recombinant Hsp70 can also correct the defects of Niemann-Pick disease type A (NPA) and type B (NPB) caused by mutations in the sphingomyelin phosphodiesterase 1 gene (SMPD1) encoding for ASM (Kirkegaard et al. 2010). Both NPA and NPB are severe lysosomal storage diseases with decreased lysosomal stability and increased lysosomal accumulation of cholesterol and sphingomyelin similar to NPC (Schuchman 2007). Recombinant Hsp70 is thought to correct the defects from ASM mutations by internalization and subsequent augmentation of lysosomal ASM activity through Hsp70 binding to BMP, thus promoting sphingomyelin-to-ceramide conversion (Kirkegaard et al. 2010). Consistently, increasing lysosomal BMP levels by thioperamide maleate reduced cholesterol overload in NPC models (Moreau et al. 2019) and amyloid deposits in aged and Alzheimer's disease tNeurons (Chou et al. 2025). However, the consistent therapeutic benefits of Hsp70 for both NPA/B and NPC indicate that Hsp70 can stabilize lysosomal membrane and alleviate lysosomal lipid storage through additional mechanisms. For example, increased Hsp70 levels may enable additional cholesterol exit pathways independent of Niemann-Pick C1 (NPC1), an established cholesterol transporter. Exploring such cholesterol exit mechanisms may open new therapeutic strategies to improve lysosomal lipid homeostasis and membrane stability in lysosomal storage disease.

In addition to genetic defects affecting lysosomal repair, chronic lysosomal stress coupled with failed repair is emerging as a key contributor to age-related pathology. The buildup of pathogenic protein aggregates, including amyloid-β, tau fibrils, and α-synuclein, is a hallmark of many degenerative diseases (Calabrese et al. 2022). Protein aggregates can cause recurrent lysosomal damage, eventually exceeding the lysosomal repair capacity, as exemplified by aggregates-mediated lysosomal damage in quiescence (Murley et al. 2025). Constitutive lysosomal damage and repair failure are observed in transdifferentiated neurons derived from aged or Alzheimer's disease fibroblasts (Chou et al. 2025). The accumulation of PI4K2A, the PITT pathway initiating enzyme, in lipofuscin-like deposits in HSP neurodegenerative models (Khundadze et al. 2021) may also reflect a failed attempt at lysosomal repair. Furthermore, the resulting lysosomal dysfunction may further exacerbate aggregate spreading and disease progression. Thus, it is important to preserve, restore, or boost lysosomal repair capacity for healthy aging and treating age-related pathologies. Interventions that increase lysosomal resilience—such as pharmacologic activation of PITT or ESCRT pathways, boosting chaperone availability (e.g., Hsp70), or modulating lysosomal lipid composition—may help slow disease progression by improving lysosomal stability. Additionally, identifying early biomarkers of lysosomal repair failure, such as persistent lysosomal galectin 3 puncta or the accumulation of deacidified lysosomes, could enable early diagnosis and therapeutic innervation. A deeper understanding of how specific repair pathways intersect with protein aggregation, lipid imbalance, and innate immune activation will be valuable for guiding combination strategies to restore lysosomal integrity and function in age-related disease.

Efficient lysosomal repair serves as a critical defense mechanism against infection, which is often exploited by pathogens to evade lysosomal degradation. For example, ESCRT-mediated lysosomal repair is inhibited by the mycobacterial type VII secretion system, with the effectors EsxG and EsxH competing with ESCRT for recruitment to damaged lysosomes (Mittal et al. 2018). While macroautophagy has established roles in microbe killing (Gutierrez et al. 2004; Nakagawa et al. 2004), lysosomal stress-induced CASM is emerging as another essential mechanism for microbe suppression (Xu et al. 2019), which is also targeted by pathogens. The *Salmonella* effector SopF ADP-ribosylates V-ATPase, disrupting its interaction with ATG16L1 and compromising the V-ATPase–ATG16L1–CASM axis, weakening host defense and promoting intracellular bacterial growth (Xu et al. 2019). Similarly, the *Legionella* effector RavZ irreversibly removes the conjugated form of ATG8 proteins from host membranes (Choy et al. 2012). RavZ is believed to enable *Legionella* growth by inhibiting autophagy (Choy et al. 2012), but recent studies indicate that it also blocks CASM (Goodwin et al. 2021; Lv et al. 2024). As CASM coordinates multiple lysosomal repair pathways, both SopF and RavZ may inhibit lysosomal repair, in addition to their established roles in blocking autophagy and TFEB activation (Goodwin et al. 2021; Lv et al. 2024; Choy et al. 2012). Thus, inhibiting bacterial or viral proteins that interfere with lysosomal repair could serve as a general therapeutic strategy for infectious disease. Additional therapeutic strategies for infection may come from pathways that protect lysosomes against pathogen-mediated damage. Upon exposure to bacterial components such as lipopolysaccharide (LPS) or peptidoglycan, or to pro-inflammatory cytokines such as IFNγ or TNF, macrophages seem to activate multiple mechanisms to enhance their lysosomal damage resistance (Wong et al. 2022). Further understanding the underlying mechanisms may open new, general strategies for combating pathogen infection.

Although efficient lysosomal repair supports healthy aging, cancer cells take advantage of it to sustain their high demand for lysosomal activity in stress clearance. For example, Hsp70 is overexpressed in many cancers (Albakova et al. 2020). Hsp70 localizes to lysosomal membranes of cancer cells where it prevents cell death by blocking LMP caused by multiple types of stressors, such as tumor necrosis factor (TNF), etoposide, and H_2O_2(Gyrd-Hansen et al. 2004). Overexpression of PI4K2A, the key enzyme in the PITT pathway, is also observed in many

cancers, where it enhances malignancy by promoting proteostasis, positioning PI4K2A as a potential target for cancer therapy (Pataer et al. 2020; Li et al. 2017, 2010). The reliance of cancer cells on high lysosomal activity creates a therapeutic opportunity to target lysosomal integrity for anticancer treatments. Indeed, cancer cells are more vulnerable to LMP inducers (Serrano-Puebla and Boya 2018). For example, cationic amphiphilic drugs (CADs) can selectively target lysosomes and induce LMP to kill cancer cells, as well as to promote lysosomal escape of other chemotherapy drugs (Nielsen et al. 2024; Petersen et al. 2013; Ellegaard et al. 2023; Groth-Pedersen and Jäättelä 2013). Likely due to the upregulation of Hsp70, an ASM activator (Kirkegaard et al. 2010), ASM itself is found to be transcriptionally downregulated across various cancers, which renders cancer cells more susceptible to ASM inhibition (Petersen et al. 2013). Given that cancer often affects senior individuals who are also susceptible to age-related degenerative diseases, precise targeting of LMP inducers to cancer cells is essential to prevent unintended lysosomal damage in non-cancerous, vulnerable cell types such as neurons.

Despite detrimental consequences of lysosomal damage, controlled LMP can have beneficial roles. In selective immune cells, LMP facilitates antigen escape from endo-lysosomal compartments into the cytosol, enabling proteasomal processing and efficient cross-presentation (Scott et al. 2025). More generally, mild, and transient lysosomal stress may trigger beneficial adaptations, leading to improved lysosomal quality, quantity, and activity. For example, trehalose, a natural disaccharide capable of ameliorating neurodegeneration, has been recently found to activate TFEB-mediated lysosomal biogenesis and autophagy upregulation through controlled lysosomal stress, including mild LMP and a modest increase in the lysosomal pH (Jeong et al. 2021; Rusmini et al. 2019). This concept, known as lysohormesis, suggests that controlled activation of lysosomal stress responses could strengthen lysosomal repair pathways and improve cellular resilience in aging and age-related diseases (Tan and Finkel 2023; Tan 2025). By stimulating key mechanisms of lysosomal repair, such as ESCRT-mediated membrane sealing, PITT-mediated lipid patching, and chaperone-mediated lysosomal stabilization, mild lysosomal stress may enhance lysosomal integrity and delay age-related cell dysfunction (Tan 2025). LMP-independent lysosomal Ca^{2+} signaling is sufficient to recruit both PITT and ESCRT components (Tan and Finkel 2022; Chen et al. 2024), suggesting that any mild lysosomal stress triggering lysosomal Ca^{2+} release could have therapeutic potential through lysohormesis. In neurodegenerative diseases, lysohormetic responses could improve lysosomal quality control, promote aggregate clearance, and slow down disease progression. Similarly, in metabolic and lysosomal storage disorders, lysohormesis may help maintain lipid homeostasis and alleviate lysosomal lipid overload. Future research should aim at establishing precise thresholds of lysosomal stress that optimize repair benefits while minimizing long-term damage.

8 | Conclusions and Perspectives

Lysosomal membrane damage is emerging as a common hallmark of aging and age-related disease, contributing to pathogenic inflammation and cell death. Given the importance of lysosomes in the clearance of a broad array of cellular stress, efficient lysosomal repair is critical for cellular health and disease prevention. The past few years have witnessed substantial progress in our understanding of lysosomal repair. Now we appreciate that a host of pathways are rapidly triggered by LMP to restore lysosomal integrity, ranging from membrane stabilization by protein condensates or oligomers, to ESCRT- and ceramide-mediated microlysophagy, to PITT-mediated lysosomal lipid remodeling and BLTP-mediated membrane patching, to membrane tubulation and recycling. Interestingly, many of these membrane repair mechanisms are not confined to lysosomes but are shared by different subcellular organelles. The ESCRT machinery is indeed more well-known for its role in the repair of the plasma membrane and nuclear envelope (Olmos 2022; Vietri et al. 2020a; Zhen et al. 2021). Similarly, most of the PITT pathway components, including PI4K2A, ORP9, ATG2, and the relevant lipids including PI4P and PS, have been recently implicated in plasma membrane repair as well (Li et al. 2024). These findings suggest a high degree of conservation and potential interplay among membrane repair pathways across organelles. The diverse lysosomal repair mechanisms highlight the dynamic and multilayered nature of cellular responses in maintaining lysosomal integrity.

Despite progress in understanding individual repair mechanisms, a major outstanding question is how these pathways are coordinated to ensure efficient lysosomal recovery. Ca^{2+} leakage is likely the initiating signal that activates multiple repair pathways including at least ESCRT, PITT, and CASM (Skowyra et al. 2018; Tan and Finkel 2022; Goodwin et al. 2021). Ca^{2+} seems to recruit ESCRT through both the Ca^{2+} effector ALG-2 (Shukla et al. 2024; Chen et al. 2024) and CASM-mediated ALIX recruitment (Corkery 2024; Huang et al. 2025), but it is still unclear which Ca^{2+} effectors activate PITT or CASM. CASM, direct Atg8ylation onto damaged lysosomes, is emerging as a central regulator linking almost all lysosomal repair processes. Additionally, galectin3 has been shown to integrate ESCRT recruitment, lysosomal ubiquitination, and lysophagy signals for optimal lysosomal recovery (Chauhan et al. 2016; Jia et al. 2020, 2018). How CASM and galectin3 coordinate different repair mechanisms remains to be further investigated.

It is important to understand how lysosomal repair pathways are affected by cellular senescence and disease. Though aging is associated with increased LMP, it remains unclear whether this is due to impaired repair efficiency or chronic lysosomal stress overwhelming repair pathways. Comparing the regulatory mechanisms of lysosomal repair in physiological and pathological contexts could open new therapeutic opportunities. Targeting lysosomal repair pathways to enhance cellular stress resilience and restore lysosomal function in aging and disease could be a promising strategy for combating age-related degeneration. Proper tire maintenance is crucial for a safe journey, and likewise, efficient lysosomal repair is essential for a smooth path to healthy aging.

Acknowledgments

We thank our Aging Institute colleagues for their discussions and comments. J.X.T. acknowledges a grant from the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health

(NIH) under the award numbers R35GM150506. We apologize to colleagues whose work we were unable to cite due to space limitations. Figures were prepared using BioRender.

Conflicts of Interest

The authors declare no conflict of interest.

Data Availability Statement

The authors have nothing to report.

References

Albakova, Z., G. A. Armeev, L. M. Kanevskiy, E. I. Kovalenko, and A. M. Sapozhnikov. 2020. "HSP70 Multi-Functionality in Cancer." *Cells* 9: 587. https://doi.org/10.3390/cells9030587.

Alberti, S., A. Gladfelter, and T. Mittag. 2019. "Considerations and Challenges in Studying Liquid-Liquid Phase Separation and Biomolecular Condensates." *Cell* 176: 419–434. https://doi.org/10.1016/j.cell.2018.12.035.

Anand, A., A. C. Mazur, P. Rosell-Arevalo, et al. 2023. "ER-Dependent Membrane Repair of Mycobacteria-Induced Vacuole Damage." *mBio* 14: e0094323. https://doi.org/10.1128/mbio.00943-23.

Appelqvist, H., L. Sandin, K. Björnström, et al. 2012. "Sensitivity to Lysosome-Dependent Cell Death Is Directly Regulated by Lysosomal Cholesterol Content." *PLoS One* 7: e50262.

Arines, F. M., A. J. Hamlin, X. Yang, Y.-Y. J. Liu, and M. Li. 2021. "A Selective Transmembrane Recognition Mechanism by a Membrane-Anchored Ubiquitin Ligase Adaptor." *Journal of Cell Biology* 220, no. 1: e202001116. https://doi.org/10.1083/jcb.202001116.

Ayala-Sanmartin, J., J. P. Henry, and L. A. Pradel. 2001. "Cholesterol Regulates Membrane Binding and Aggregation by Annexin 2 at Submicromolar Ca2+ Concentration." *Biochimica et Biophysica Acta (BBA) - Biomembranes* 1510: 18–28. https://doi.org/10.1016/s0005-2736(00)00262-5.

Bentley-DeSousa, A., D. Clegg, and S. M. Ferguson. 2025a. "LRRK2, Lysosome Damage, and Parkinson's Disease." *Current Opinion in Cell Biology* 93: 102482. https://doi.org/10.1016/j.ceb.2025.102482.

Bentley-DeSousa, A., A. Roczniak-Ferguson, and S. M. Ferguson. 2025b. "A STING–CASM–GABARAP Pathway Activates LRRK2 at Lysosomes." *Journal of Cell Biology* 224, no. 2: e202310150. https://doi.org/10.1083/jcb.202310150.

Bhattacharya, A., R. Mukherjee, S. K. Kuncha, et al. 2023. "A Lysosome Membrane Regeneration Pathway Depends on TBC1D15 and Autophagic Lysosomal Reformation Proteins." *Nature Cell Biology* 25: 685–698. https://doi.org/10.1038/s41556-023-01125-9.

Blackwood, R. A., and J. D. Ernst. 1990. "Characterization of Ca2(+)-dependent Phospholipid Binding, Vesicle Aggregation and Membrane Fusion by Annexins." *Biochemical Journal* 266: 195–200. https://doi.org/10.1042/bj2660195.

Bonet-Ponce, L., A. Beilina, C. D. Williamson, et al. 2020. "LRRK2 Mediates Tubulation and Vesicle Sorting From Lysosomes." *Science Advances* 6: eabb2454. https://doi.org/10.1126/sciadv.abb2454.

Bonet-Ponce, L., and M. R. Cookson. 2022. "The Endoplasmic Reticulum Contributes to Lysosomal Tubulation/Sorting Driven by LRRK2." *Molecular Biology of the Cell* 33: ar124.

Bouter, A., C. Gounou, R. Bérat, et al. 2011. "Annexin-A5 Assembled Into Two-Dimensional Arrays Promotes Cell Membrane Repair." *Nature Communications* 2: 270. https://doi.org/10.1038/ncomms1270.

Boye, T. L., K. Maeda, W. Pezeshkian, et al. 2017. "Annexin A4 and A6 Induce Membrane Curvature and Constriction During Cell Membrane Repair." *Nature Communications* 8: 1623. https://doi.org/10.1038/s41467-017-01743-6.

Boyle, K. B., C. J. Ellison, P. R. Elliott, et al. 2023. "TECPR1 Conjugates LC3 to Damaged Endomembranes Upon Detection of Sphingomyelin Exposure." *EMBO Journal* 42: e113012. https://doi.org/10.15252/embj.2022113012.

Brady, R. O., J. N. Kanfer, M. B. Mock, and D. S. Fredrickson. 1966. "The Metabolism of Sphingomyelin. II. Evidence of an Enzymatic Deficiency in Niemann-Pick Diseae." *Proceedings of the National Academy of Sciences* 55: 366–369. https://doi.org/10.1073/pnas.55.2.366.

Bussi, C., A. Mangiarotti, C. Vanhille-Campos, et al. 2023. "Stress Granules Plug and Stabilize Damaged Endolysosomal Membranes." *Nature* 623: 1062–1069. https://doi.org/10.1038/s41586-023-06726-w.

Cabukusta, B., and J. Neefjes. 2018. "Mechanisms of Lysosomal Positioning and Movement." *Traffic* 19: 761–769. https://doi.org/10.1111/tra.12587.

Calabrese, G., C. Molzahn, and T. Mayor. 2022. "Protein Interaction Networks in Neurodegenerative Diseases: From Physiological Function to Aggregation." *Journal of Biological Chemistry* 298: 102062. https://doi.org/10.1016/j.jbc.2022.102062.

Calvaresi, V., L. T. Truelsen, S. B. Larsen, N. H. T. Petersen, T. Kirkegaard, and K. D. Rand. 2021. "Conformational Dynamics of Free and Membrane-Bound Human Hsp70 in Model Cytosolic and Endo-Lysosomal Environments." *Communications Biology* 4: 1369. https://doi.org/10.1038/s42003-021-02892-7.

Carling, G. K., L. Fan, N. R. Foxe, et al. 2024. "Alzheimer's Disease-Linked Risk Alleles Elevate Microglial cGAS-Associated Senescence and Neurodegeneration in a Tauopathy Model." *Neuron* 112: e3878. https://doi.org/10.1016/j.neuron.2024.09.006.

Chauhan, S., S. Kumar, A. Jain, et al. 2016. "TRIMs and Galectins Globally Cooperate and TRIM16 and galectin-3 Co-Direct Autophagy in Endomembrane Damage Homeostasis." *Developmental Cell* 39: 13–27.

Chen, H., J. Yang, P. S. Low, and J. X. Cheng. 2008. "Cholesterol Level Regulates Endosome Motility via Rab Proteins." *Biophysical Journal* 94: 1508–1520. https://doi.org/10.1529/biophysj.106.099366.

Chen, J. J., D. L. Nathaniel, P. Raghavan, et al. 2019. "Compromised Function of the ESCRT Pathway Promotes Endolysosomal Escape of Tau Seeds and Propagation of Tau Aggregation." *Journal of Biological Chemistry* 294: 18952–18966.

Chen, W., M. M. Motsinger, J. Li, K. P. Bohannon, and P. I. Hanson. 2024. "Ca(2+)-sensor ALG-2 Engages ESCRTs to Enhance Lysosomal Membrane Resilience to Osmotic Stress." *Proceedings of the National Academy of Sciences* 121: e2318412121. https://doi.org/10.1073/pnas.2318412121.

Chou, C.-C., R. Vest, M. A. Prado, et al. 2025. "Proteostasis and Lysosomal Repair Deficits in Transdifferentiated Neurons of Alzheimer's Disease." *Nature Cell Biology* 27: 619–632. https://doi.org/10.1038/s41556-025-01623-y.

Choy, A., J. Dancourt, B. Mugo, et al. 2012. "The Legionella Effector RavZ Inhibits Host Autophagy Through Irreversible Atg8 Deconjugation." *Science* 338: 1072–1076. https://doi.org/10.1126/science.1227026.

Claude-Taupin, A., J. Jia, Z. Bhujabal, et al. 2021. "ATG9A Protects the Plasma Membrane From Programmed and Incidental Permeabilization." *Nature Cell Biology* 23: 846–858. https://doi.org/10.1038/s41556-021-00706-w.

Corkery, D. P., et al. 2024. "ESCRT Recruitment to Damaged Lysosomes Is Dependent on the ATG8 E3-Like Ligases." *bioRxiv*. https://doi.org/10.1101/2024.04.30.591897.

Corkery, D. P., S. Castro-Gonzalez, A. Knyazeva, L. K. Herzog, and Y. W. Wu. 2023. "An ATG12-ATG5-TECPR1 E3-like Complex Regulates Unconventional LC3 Lipidation at Damaged Lysosomes." *EMBO Reports* 24: e56841. https://doi.org/10.15252/embr.202356841.

Cross, J., J. Durgan, D. G. McEwan, M. Tayler, K. M. Ryan, and O. Florey. 2023. "Lysosome Damage Triggers Direct ATG8 Conjugation

and ATG2 Engagement via Non-Canonical Autophagy." *Journal of Cell Biology* 222, no. 12: e202303078. https://doi.org/10.1083/jcb.202303078.

Davis, D. B., K. R. Doherty, A. J. Delmonte, and E. M. McNally. 2002. "Calcium-Sensitive Phospholipid Binding Properties of Normal and Mutant Ferlin C2 Domains." *Journal of Biological Chemistry* 277: 22883–22888. https://doi.org/10.1074/jbc.M201858200.

Delfosse, V., W. Bourguet, and G. Drin. 2020. "Structural and Functional Specialization of OSBP-Related Proteins." *Contact* 3: 251525642094662.

Demonbreun, A. R., M. Quattrocelli, D. Y. Barefield, M. V. Allen, K. E. Swanson, and E. M. McNally. 2016. "An Actin-Dependent Annexin Complex Mediates Plasma Membrane Repair in Muscle." *Journal of Cell Biology* 213: 705–718. https://doi.org/10.1083/jcb.201512022.

Deretic, V., T. Duque, E. Trosdal, M. Paddar, R. Javed, and P. Akepati. 2024. "Membrane atg8ylation in Canonical and Noncanonical Autophagy." *Journal of Molecular Biology* 436: 168532. https://doi.org/10.1016/j.jmb.2024.168532.

Doherty, K. R., A. Cave, D. B. Davis, et al. 2005. "Normal Myoblast Fusion Requires Myoferlin." *Development* 132: 5565–5575. https://doi.org/10.1242/dev.02155.

Drücker, P., M. Pejic, D. Grill, H.-J. Galla, and V. Gerke. 2014. "Cooperative Binding of Annexin A2 to Cholesterol-and phosphatidylinositol-4, 5-bisphosphate-containing Bilayers." *Biophysical Journal* 107: 2070–2081.

Duran, J., J. E. Salinas, R. Wheaton, et al. 2024. "Calcium Signaling From Damaged Lysosomes Induces Cytoprotective Stress Granules." *The EMBO Journal* 43: 6410–6443. https://doi.org/10.1038/s44318-024-00292-1.

Durgan, J., and O. Florey. 2022. "Many Roads Lead to Casm: Diverse Stimuli of Noncanonical Autophagy Share a Unifying Molecular Mechanism." *Science Advances* 8: eabo1274. https://doi.org/10.1126/sciadv.abo1274.

Durgan, J., A. H. Lystad, K. Sloan, et al. 2021. "Non-Canonical Autophagy Drives Alternative ATG8 Conjugation to Phosphatidylserine." *Molecular Cell* 81: e2038. https://doi.org/10.1016/j.molcel.2021.03.020.

Ebstrup, M. L., S. L. Sønder, D. L. Fogde, et al. 2024. "Annexin A7 Mediates Lysosome Repair Independently of ESCRT-III." *Frontiers in Cell and Developmental Biology* 11: 1211498. https://doi.org/10.3389/fcell.2023.1211498.

Eguchi, T., T. Kuwahara, M. Sakurai, et al. 2018. "LRRK2 and Its Substrate Rab Gtpases Are Sequentially Targeted Onto Stressed Lysosomes and Maintain Their Homeostasis." *Proceedings of the National Academy of Sciences* 115: E9115–E9124. https://doi.org/10.1073/pnas.1812196115.

Eguchi, T., M. Sakurai, Y. Wang, et al. 2024. "The V-ATPase-ATG16L1 Axis Recruits LRRK2 to Facilitate the Lysosomal Stress Response." *Journal of Cell Biology* 223, no. 3: e202302067. https://doi.org/10.1083/jcb.202302067.

Ellegaard, A. M., P. Bach, and M. Jäättelä. 2023. "Targeting Cancer Lysosomes With Good Old Cationic Amphiphilic Drugs." *Reviews of Physiology Biochemistry and Pharmacology* 185: 107–152. https://doi.org/10.1007/112_2020_56.

Ellison, C. J., W. Kukulski, K. B. Boyle, S. Munro, and F. Randow. 2020. "Transbilayer Movement of Sphingomyelin Precedes Catastrophic Breakage of Enterobacteria-Containing Vacuoles." *Current Biology* 30: e2976.

Eriksson, I., P. Wäster, and K. Öllinger. 2020. "Restoration of Lysosomal Function After Damage Is Accompanied by Recycling of Lysosomal Membrane Proteins." *Cell Death & Disease* 11: 1–16.

Fischer, T. D., C. Wang, B. S. Padman, M. Lazarou, and R. J. Youle. 2020. "Sting Induces LC3B Lipidation Onto Single-Membrane Vesicles via the V-ATPase and ATG16L1-WD40 Domain." *Journal of Cell Biology* 219, no. 12: e202009128. https://doi.org/10.1083/jcb.202009128.

Florey, O., N. Gammoh, S. E. Kim, X. Jiang, and M. Overholtzer. 2015. "V-ATPase and Osmotic Imbalances Activate Endolysosomal LC3 Lipidation." *Autophagy* 11: 88–99.

Gabandé-Rodríguez, E., P. Boya, V. Labrador, C. G. Dotti, and M. D. Ledesma. 2014. "High Sphingomyelin Levels Induce Lysosomal Damage and Autophagy Dysfunction in Niemann Pick Disease Type A." *Cell Death & Differentiation* 21: 864–875. https://doi.org/10.1038/cdd.2014.4.

Gahlot, P., B. Kravic, G. Rota, et al. 2024. "Lysosomal Damage Sensing and Lysophagy Initiation by SPG20-ITCH." *Molecular Cell* 84: e1510. https://doi.org/10.1016/j.molcel.2024.02.029.

Ghanbarpour, A., D. P. Valverde, T. J. Melia, and K. M. Reinisch. 2021. "A Model for a Partnership of Lipid Transfer Proteins and Scramblases in Membrane Expansion and Organelle Biogenesis." *Proceedings of the National Academy of Sciences* 118: e2101562118. https://doi.org/10.1073/pnas.2101562118.

Gómez-Sintes, R., M. D. Ledesma, and P. Boya. 2016. "Lysosomal Cell Death Mechanisms in Aging." *Ageing Research Reviews* 32: 150–168.

Goodwin, J. M., W. G. Walkup, K. Hooper, et al. 2021. "GABARAP Sequesters the FLCN-FNIP Tumor Suppressor Complex to Couple Autophagy With Lysosomal Biogenesis." *Science Advances* 7: eabj2485.

Gray, J., M. E. Fernández-Suárez, M. Falah, et al. 2022. "Heat Shock Protein Amplification Improves Cerebellar Myelination in the Npc1(nih) Mouse Model." *EBioMedicine* 86: 104374. https://doi.org/10.1016/j.ebiom.2022.104374.

Gros, F., and S. Muller. 2023. "The Role of Lysosomes in Metabolic and Autoimmune Diseases." *Nature Reviews Nephrology* 19: 366–383. https://doi.org/10.1038/s41581-023-00692-2.

Groth-Pedersen, L., and M. Jäättelä. 2013. "Combating Apoptosis and Multidrug Resistant Cancers by Targeting Lysosomes." *Cancer Letters* 332: 265–274. https://doi.org/10.1016/j.canlet.2010.05.021.

Gulen, M. F., N. Samson, A. Keller, et al. 2023. "cGAS-STING Drives Ageing-Related Inflammation and Neurodegeneration." *Nature* 620: 374–380. https://doi.org/10.1038/s41586-023-06373-1.

Gupta, S., J. Yano, V. Mercier, et al. 2021. "Lysosomal Retargeting of Myoferlin Mitigates Membrane Stress to Enable Pancreatic Cancer Growth." *Nature Cell Biology* 23: 232–242. https://doi.org/10.1038/s41556-021-00644-7.

Gutierrez, E. M., N. A. Seebacher, L. Arzuman, et al. 2016. "Lysosomal Membrane Stability Plays a Major Role In the Cytotoxic Activity of the Anti-Proliferative Agent, Di-2-Pyridylketone 4, 4-Dimethyl-3-Thiosemicarbazone (Dp44mt)." *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* 1863: 1665–1681.

Gutierrez, M. G., S. S. Master, S. B. Singh, G. A. Taylor, M. I. Colombo, and V. Deretic. 2004. "Autophagy Is a Defense Mechanism Inhibiting BCG and Mycobacterium Tuberculosis Survival in Infected Macrophages." *Cell* 119: 753–766. https://doi.org/10.1016/j.cell.2004.11.038.

Gyrd-Hansen, M., J. Nylandsted, and M. Jäättelä. 2004. "Heat Shock Protein 70 Promotes Cancer Cell Viability by Safeguarding Lysosomal Integrity." *Cell Cycle* 3: 1484–1485. https://doi.org/10.4161/cc.3.12.1287.

Hancock-Cerutti, W., Z. Wu, P. Xu, et al. 2022. "Er-Lysosome Lipid Transfer Protein VPS13C/PARK23 Prevents Aberrant mtDNA-Dependent Sting Signaling." *Journal of Cell Biology* 221, no. 7: e202106046. https://doi.org/10.1083/jcb.202106046.

Hanna, M. G., et al. 2024. "Bridge-Like Lipid Transfer Protein 3A (BLTP3A) Is Associated With Membranes of the Late Endocytic Pathway and Is an Effector of CASM." *bioRxiv*. https://doi.org/10.1101/2024.09.28.615015.

Henn, D., X. Yang, and M. Li. 2025. "Lysosomal Quality Control Review." *Autophagy*: 1–20. https://doi.org/10.1080/15548627.2025.2469206.

Herbst, S., P. Campbell, J. Harvey, et al. 2020. "LRRK2 Activation Controls the Repair of Damaged Endomembranes in Macrophages." *EMBO Journal* 39: e104494. https://doi.org/10.15252/embj.2020104494.

Hooper, K. M., E. Jacquin, T. Li, et al. 2022. "V-ATPase Is a Universal Regulator of LC3-associated Phagocytosis and Non-Canonical Autophagy." *Journal of Cell Biology* 221, no. 6: e202105112. https://doi.org/10.1083/jcb.202105112.

Huang, D., B. Xu, L. Liu, et al. 2021. "TMEM41B Acts as an ER Scramblase Required for Lipoprotein Biogenesis and Lipid Homeostasis." *Cell Metabolism* 33: e1658. https://doi.org/10.1016/j.cmet.2021.05.006.

Huang, T., C. Sun, F. Du, and Z. J. Chen. 2025. "Sting-Induced Noncanonical Autophagy Regulates Endolysosomal Homeostasis." *Proceedings of the National Academy of Sciences* 122: e2415422122. https://doi.org/10.1073/pnas.2415422122.

Hung, Y.-H., L. M.-W. Chen, J.-Y. Yang, and W. Yuan Yang. 2013. "Spatiotemporally Controlled Induction of Autophagy-Mediated Lysosome Turnover." *Nature Communications* 4: 2111.

Ichimura, Y., T. Kirisako, T. Takao, et al. 2000. "A Ubiquitin-Like System Mediates Protein Lipidation." *Nature* 408: 488–492. https://doi.org/10.1038/35044114.

Javed, R., A. Jain, T. Duque, et al. 2023. "Mammalian ATG8 Proteins Maintain Autophagosomal Membrane Integrity Through ESCRTs." *EMBO Journal* 42: e112845. https://doi.org/10.15252/embj.2022112845.

Jeong, E., R. Willett, A. Rissone, M. La Spina, and R. Puertollano. 2024. "TMEM55B Links Autophagy Flux, Lysosomal Repair, and TFE3 Activation in Response to Oxidative Stress." *Nature Communications* 15: 93. https://doi.org/10.1038/s41467-023-44316-6.

Jeong, S. J., J. Stitham, T. D. Evans, et al. 2021. "Trehalose Causes Low-Grade Lysosomal Stress to Activate Tfeb and the Autophagy-Lysosome Biogenesis Response." *Autophagy* 17: 3740–3752. https://doi.org/10.1080/15548627.2021.1896906.

Jia, J., Y. P. Abudu, A. Claude-Taupin, et al. 2018. "Galectins Control mTOR in Response to Endomembrane Damage." *Molecular Cell* 70: e128.

Jia, J., A. Claude-Taupin, Y. Gu, et al. 2020. "Galectin-3 Coordinates a Cellular System for Lysosomal Repair and Removal." *Developmental Cell* 52: e68.

Jia, J., S. Poolsup, and J. E. Salinas. 2025. "Cellular Homeostatic Responses to Lysosomal Damage." *Trends in Cell Biology*. https://doi.org/10.1016/j.tcb.2025.02.007.

Jia, J., F. Wang, Z. Bhujabal, et al. 2022. "Stress Granules and Mtor Are Regulated by Membrane atg8ylation During Lysosomal Damage." *Journal of Cell Biology* 221, no. 11: e202207091. https://doi.org/10.1083/jcb.202207091.

Kaur, N., L. R. de la Ballina, H. S. Haukaas, et al. 2023. "TECPR1 Is Activated by Damage-Induced Sphingomyelin Exposure to Mediate Noncanonical Autophagy." *EMBO Journal* 42: e113105. https://doi.org/10.15252/embj.2022113105.

Khundadze, M., F. Ribaudo, A. Hussain, et al. 2021. "Mouse Models for Hereditary Spastic Paraplegia Uncover a Role of PI4K2A in Autophagic Lysosome Reformation." *Autophagy* 17: 3690–3706. https://doi.org/10.1080/15548627.2021.1891848.

Kirkegaard, T., A. G. Roth, N. H. T. Petersen, et al. 2010. "Hsp70 Stabilizes Lysosomes and Reverts Niemann-Pick Disease-Associated Lysosomal Pathology." *Nature* 463: 549–553. https://doi.org/10.1038/nature08710.

Klein, A. D., K. L. Petruzzi, C. Lee, and M. Overholtzer. 2024. "Stress-Induced Microautophagy Is Coordinated With Lysosome Biogenesis and Regulated by PIKfyve." *Molecular Biology of the Cell* 35: ar70. https://doi.org/10.1091/mbc.E23-08-0332.

Koerver, L., C. Papadopoulos, B. Liu, et al. 2019. "The Ubiquitin-Conjugating Enzyme Ube 2 QL 1 Coordinates Lysophagy in Response to Endolysosomal Damage." *EMBO Reports* 20: e48014.

Kravić, B., T. Bionda, A. Siebert, et al. 2022. "Ubiquitin Profiling of Lysophagy Identifies Actin Stabilizer CNN2 as a Target of VCP/p97 and Uncovers a Link to HSPB1." *Molecular Cell* 82: e2637.

Kumar, S., A. Jain, S. W. Choi, et al. 2020. "Mammalian Atg8 Proteins and the Autophagy Factor IRGM Control mTOR and TFEB at a Regulatory Node Critical for Responses to Pathogens." *Nature Cell Biology* 22: 973–985.

Kumar, S., J. Jia, and V. Deretic. 2021. "Atg8ylation as a General Membrane Stress and Remodeling Response." *Cell Stress* 5: 128–142. https://doi.org/10.15698/cst2021.09.255.

Lee, C., L. Lamech, E. Johns, and M. Overholtzer. 2020. "Selective Lysosome Membrane Turnover Is Induced by Nutrient Starvation." *Developmental Cell* 55: e284. https://doi.org/10.1016/j.devcel.2020.08.008.

Lennon, N. J., A. Kho, B. J. Bacskai, S. L. Perlmutter, B. T. Hyman, and R. H. Brown. 2003. "Dysferlin Interacts With Annexins A1 and A2 and Mediates Sarcolemmal Wound-Healing." *Journal of Biological Chemistry* 278: 50466–50473. https://doi.org/10.1074/jbc.M307247200.

Li, J., Z. Gao, D. Zhao, et al. 2017. "PI-273, a Substrate-Competitive, Specific Small-Molecule Inhibitor of PI4KIIα, Inhibits the Growth of Breast Cancer Cells." *Cancer Research* 77: 6253–6266.

Li, J., Y. Lu, J. Zhang, H. Kang, Z. Qin, and C. Chen. 2010. "PI4KIIα Is a Novel Regulator of Tumor Growth by Its Action on Angiogenesis and HIF-1α Regulation." *Oncogene* 29: 2550–2559.

Li, M., T. Koshi, and S. D. Emr. 2015b. "Membrane-Anchored Ubiquitin Ligase Complex Is Required for the Turnover of Lysosomal Membrane Proteins." *Journal of Cell Biology* 211: 639–652.

Li, M., Y. Rong, Y.-S. Chuang, D. Peng, and S. D. Emr. 2015a. "Ubiquitin-Dependent Lysosomal Membrane Protein Sorting and Degradation." *Molecular Cell* 57: 467–478.

Li, P., M. Gu, and H. Xu. 2019. "Lysosomal Ion Channels as Decoders of Cellular Signals." *Trends in Biochemical Sciences* 44: 110–124. https://doi.org/10.1016/j.tibs.2018.10.006.

Li, X., N. Rydzewski, A. Hider, et al. 2016. "A Molecular Mechanism to Regulate Lysosome Motility for Lysosome Positioning and Tubulation." *Nature Cell Biology* 18: 404–417. https://doi.org/10.1038/ncb3324.

Li, Y. E., D. M. Norris, F. N. Xiao, et al. 2024. "Phosphatidylserine Regulates Plasma Membrane Repair Through Tetraspanin-Enriched Macrodomains." *Journal of Cell Biology* 223, no. 6: e202307041. https://doi.org/10.1083/jcb.202307041.

Li, Y. E., Y. Wang, X. Du, et al. 2021. "TMEM41B and VMP1 Are Scramblases and Regulate the Distribution of Cholesterol and Phosphatidylserine." *Journal of Cell Biology* 220, no. 6: e202103105. https://doi.org/10.1083/jcb.202103105.

Lim, C. Y., O. B. Davis, H. R. Shin, et al. 2019. "ER-Lysosome Contacts Enable Cholesterol Sensing by mTORC1 and Drive Aberrant Growth Signalling in Niemann-Pick Type C." *Nature Cell Biology* 21: 1206–1218. https://doi.org/10.1038/s41556-019-0391-5.

Liu, B., R. J. Carlson, I. S. Pires, et al. 2023. "Human Sting Is a Proton Channel." *Science* 381: 508–514. https://doi.org/10.1126/science.adf8974.

Lv, B., W. A. Dion, H. Yang, et al. 2024. "A TBK1-independent Primordial Function of Sting in Lysosomal Biogenesis." *Molecular Cell* 84: 3979–3996.e9. https://doi.org/10.1016/j.molcel.2024.08.026.

Maeda, S., C. Otomo, and T. Otomo. 2019. "The Autophagic Membrane Tether ATG2A Transfers Lipids Between Membranes." *eLife* 8: e45777.

Maejima, I., A. Takahashi, H. Omori, et al. 2013. "Autophagy Sequesters Damaged Lysosomes to Control Lysosomal Biogenesis and Kidney Injury." *EMBO Journal* 32: 2336–2347.

De Maio, A. 2014. "Extracellular Hsp70: Export and Function." *Current Protein & Peptide Science* 15: 225–231. https://doi.org/10.2174/1389203715666140331113057.

Martina, J. A., H. I. Diab, L. Lishu, et al. 2014. "The Nutrient-Responsive Transcription Factor TFE3 Promotes Autophagy, Lysosomal

Biogenesis, and Clearance of Cellular Debris." *Science Signaling* 7, no. 9: ra9. https://doi.org/10.1126/scisignal.2004754.

Matoba, K., T. Kotani, A. Tsutsumi, et al. 2020. "Atg9 Is a Lipid Scramblase That Mediates Autophagosomal Membrane Expansion." *Nature Structural & Molecular Biology* 27: 1185–1193.

Mesmin, B., J. Bigay, J. Moser von Filseck, S. Lacas-Gervais, G. Drin, and B. Antonny. 2013. "A Four-Step Cycle Driven by PI (4) P Hydrolysis Directs Sterol/Pi (4) P Exchange by the ER-Golgi Tether OSBP." *Cell* 155: 830–843.

Meyer, H., and B. Kravic. 2024. "The Endo-Lysosomal Damage Response." *Annual Review of Biochemistry* 93: 367–387. https://doi.org/10.1146/annurev-biochem-030222-102505.

Mittal, E., M. L. Skowyra, G. Uwase, et al. 2018. "Mycobacterium Tuberculosis Type VII Secretion System Effectors Differentially Impact the ESCRT Endomembrane Damage Response." *mBio* 9: e01765-01718.

Mizushima, N., A. Kuma, Y. Kobayashi, et al. 2003. "Mouse Apg16L, a Novel Wd-Repeat Protein, Targets to the Autophagic Isolation Membrane With the Apg12-Apg5 Conjugate." *Journal of Cell Science* 116: 1679–1688. https://doi.org/10.1242/jcs.00381.

Moreau, D., F. Vacca, S. Vossio, et al. 2019. "Drug-Induced Increase in Lysobisphosphatidic Acid Reduces the Cholesterol Overload in Niemann-Pick Type C Cells and Mice." *EMBO Reports* 20: e47055. https://doi.org/10.15252/embr.201847055.

Murley, A., A. C. Popovici, X. S. Hu, et al. 2025. "Quiescent Cell Re-Entry Is Limited by Macroautophagy-Induced Lysosomal Damage." *Cell*. https://doi.org/10.1016/j.cell.2025.03.009.

Nakagawa, I., A. Amano, N. Mizushima, et al. 2004. "Autophagy Defends Cells Against Invading Group A Streptococcus." *Science* 306: 1037–1040. https://doi.org/10.1126/science.1103966.

Nakamura, S., S. Shigeyama, S. Minami, et al. 2020. "LC3 Lipidation Is Essential for TFEB Activation During the Lysosomal Damage Response to Kidney Injury." *Nature Cell Biology* 22: 1252–1263.

Napolitano, G., and A. Ballabio. 2016. "TFEB at a Glance." *Journal of Cell Science* 129: 2475–2481. https://doi.org/10.1242/jcs.146365.

Neuman, S. D., T. P. Levine, and A. Bashirullah. 2022. "A Novel Superfamily of Bridge-Like Lipid Transfer Proteins." *Trends in Cell Biology* 32: 962–974. https://doi.org/10.1016/j.tcb.2022.03.011.

Niekamp, P., F. Scharte, T. Sokoya, et al. 2022. "Ca(2+)-activated Sphingomyelin Scrambling and Turnover Mediate Escrt-Independent Lysosomal Repair." *Nature Communications* 13: 1875. https://doi.org/10.1038/s41467-022-29481-4.

Nielsen, I. Ø., K. K. B. Clemmensen, D. L. Fogde, et al. 2024. "Cationic Amphiphilic Drugs Induce Accumulation of Cytolytic Lysoglycerophospholipids in the Lysosomes of Cancer Cells and Block Their Recycling Into Common Membrane Glycerophospholipids." *Molecular Biology of the Cell* 35: ar25. https://doi.org/10.1091/mbc.E23-06-0263.

Ogura, M., T. Kaminishi, T. Shima, et al. 2023. "Microautophagy Regulated by STK38 and GABARAPs Is Essential to Repair Lysosomes and Prevent Aging." *EMBO Reports* 24: e57300. https://doi.org/10.15252/embr.202357300.

Olmos, Y. 2022. "The ESCRT Machinery: Remodeling, Repairing, and Sealing Membranes." *Membranes* 12: 633. https://doi.org/10.3390/membranes12060633.

Osawa, T., Y. Ishii, and N. N. Noda. 2020. "Human ATG2B Possesses a Lipid Transfer Activity Which Is Accelerated by Negatively Charged Lipids and WIPI4." *Genes to Cells* 25: 65–70.

Osawa, T., T. Kotani, T. Kawaoka, et al. 2019. "Atg2 Mediates Direct Lipid Transfer Between Membranes for Autophagosome Formation." *Nature Structural & Molecular Biology* 26: 281–288.

Pataer, A., B. Ozpolat, R. Shao, et al. 2020. "Therapeutic Targeting of the PI4K2A/PKR Lysosome Network Is Critical for Misfolded Protein Clearance and Survival in Cancer Cells." *Oncogene* 39: 801–813.

Peng, K., G. Zhao, H. Zhao, N. N. Noda, and H. Zhang. 2025. "The Autophagy Protein ATG-9 Regulates Lysosome Function and Integrity." *Journal of Cell Biology* 224, no. 6: e202411092. https://doi.org/10.1083/jcb.202411092.

Petersen, N. H. T., T. Kirkegaard, O. D. Olsen, and M. Jäättelä. 2010. "Connecting Hsp70, Sphingolipid Metabolism and Lysosomal Stability." *Cell Cycle* 9: 2305–2309. https://doi.org/10.4161/cc.9.12.12052.

Petersen, N. H. T., O. D. Olsen, L. Groth-Pedersen, et al. 2013. "Transformation-Associated Changes in Sphingolipid Metabolism Sensitize Cells to Lysosomal Cell Death Induced by Inhibitors of Acid Sphingomyelinase." *Cancer Cell* 24: 379–393. https://doi.org/10.1016/j.ccr.2013.08.003.

Pipalia, N. H., S. Z. Saad, K. Subramanian, et al. 2021. "HSP90 Inhibitors Reduce Cholesterol Storage in Niemann-Pick Type C1 Mutant Fibroblasts." *Journal of Lipid Research* 62: 100114. https://doi.org/10.1016/j.jlr.2021.100114.

Puhka, M., H. Vihinen, M. Joensuu, and E. Jokitalo. 2007. "Endoplasmic Reticulum Remains Continuous and Undergoes Sheet-to-Tubule Transformation During Cell Division in Mammalian Cells." *Journal of Cell Biology* 179: 895–909. https://doi.org/10.1083/jcb.200705112.

Radulovic, M., K. O. Schink, E. M. Wenzel, et al. 2018. "ESCRT-Mediated Lysosome Repair Precedes Lysophagy and Promotes Cell Survival." *EMBO Journal* 37: e99753.

Radulovic, M., E. M. Wenzel, S. Gilani, et al. 2022. "Cholesterol Transfer via Endoplasmic Reticulum Contacts Mediates Lysosome Damage Repair." *EMBO Journal* 41: e112677. https://doi.org/10.15252/embj.2022112677.

Rayens, N. T., K. J. Cook, S. A. McKinley, and C. K. Payne. 2022. "Transport of Lysosomes Decreases in the Perinuclear Region: Insights From Changepoint Analysis." *Biophysical Journal* 121: 1205–1218. https://doi.org/10.1016/j.bpj.2022.02.032.

Rocha, E. M., M. T. Keeney, R. Di Maio, B. R. De Miranda, and J. T. Greenamyre. 2022. "LRRK2 and Idiopathic Parkinson's Disease." *Trends in Neurosciences* 45: 224–236. https://doi.org/10.1016/j.tins.2021.12.002.

Rovira, M., R. Sereda, D. Pladevall-Morera, et al. 2022. "The Lysosomal Proteome of Senescent Cells Contributes to the Senescence Secretome." *Aging Cell* 21: e13707. https://doi.org/10.1111/acel.13707.

Rusmini, P., K. Cortese, V. Crippa, et al. 2019. "Trehalose Induces Autophagy via Lysosomal-Mediated Tfeb Activation in Models of Motoneuron Degeneration." *Autophagy* 15: 631–651. https://doi.org/10.1080/15548627.2018.1535292.

Scharf, B., C. C. Clement, X. X. Wu, et al. 2012. "Annexin A2 Binds to Endosomes Following Organelle Destabilization by Particulate Wear Debris." *Nature Communications* 3: 755. https://doi.org/10.1038/ncomms1754.

Scheffer, L. L., S. C. Sreetama, N. Sharma, et al. 2014. "Mechanism of Ca2+-triggered ESCRT Assembly and Regulation of Cell Membrane Repair." *Nature Communications* 5: 5646. https://doi.org/10.1038/ncomms6646.

Schuchman, E. H. 2007. "The Pathogenesis and Treatment of Acid Sphingomyelinase-Deficient Niemann-Pick Disease." *Journal of Inherited Metabolic Disease* 30: 654–663. https://doi.org/10.1007/s10545-007-0632-9.

Scott, O., E. Saran, and S. A. Freeman. 2025. "The Spectrum of Lysosomal Stress and Damage Responses: From Mechanosensing to Inflammation." *EMBO Reports* 26: 1425–1439. https://doi.org/10.1038/s44319-025-00405-9.

Serrano-Puebla, A., and P. Boya. 2018. "Lysosomal Membrane Permeabilization as a Cell Death Mechanism in Cancer Cells." *Biochemical Society Transactions* 46: 207–215. https://doi.org/10.1042/bst20170130.

Shen, D., X. Wang, X. Li, et al. 2012. “Lipid Storage Disorders Block Lysosomal Trafficking by Inhibiting a TRP Channel and Lysosomal Calcium Release.” *Nature Communications* 3: 731. https://doi.org/10.1038/ncomms1735.

Shukla, S., W. Chen, S. Rao, et al. 2024. “Mechanism and Cellular Function of Direct Membrane Binding by the ESCRT and ERES-Associated Ca(2+)-sensor ALG-2.” *Proceedings of the National Academy of Sciences* 121: e2318046121. https://doi.org/10.1073/pnas.2318046121.

Shukla, S., K. P. Larsen, C. Ou, K. Rose, and J. H. Hurley. 2022. “In Vitro Reconstitution of Calcium-Dependent Recruitment of the Human ESCRT Machinery in Lysosomal Membrane Repair.” *Proceedings of the National Academy of Sciences* 119: e2205590119. https://doi.org/10.1073/pnas.2205590119.

Simons, J. P., R. Al-Shawi, S. Minogue, et al. 2009. “Loss of Phosphatidylinositol 4-kinase 2α Activity Causes Late Onset Degeneration of Spinal Cord Axons.” *Proceedings of the National Academy of Sciences* 106: 11535–11539. https://doi.org/10.1073/pnas.0903011106.

Skowyra, M. L., P. H. Schlesinger, T. V. Naismith, and P. I. Hanson. 2018. “Triggered Recruitment of ESCRT Machinery Promotes Endolysosomal Repair.” *Science* 360: eaar5078.

Sliter, D. A., J. Martinez, L. Hao, et al. 2018. “Parkin and PINK1 Mitigate Sting-Induced Inflammation.” *Nature* 561: 258–262. https://doi.org/10.1038/s41586-018-0448-9.

Tan, J. X. 2025. “Harnessing Lysohormesis for Healthy Ageing.” *Nature Cell Biology* 27: 548–551. https://doi.org/10.1038/s41556-025-01634-9.

Tan, J. X., and T. Finkel. 2022. “A Phosphoinositide Signalling Pathway Mediates Rapid Lysosomal Repair.” *Nature* 609: 815–821. https://doi.org/10.1038/s41586-022-05164-4.

Tan, J. X., and T. Finkel. 2023. “Lysosomes in Senescence and Aging.” *EMBO Reports* 24: e57265. https://doi.org/10.15252/embr.202357265.

Teranishi, H., K. Tabata, M. Saeki, et al. 2022. “Identification of CUL4A-DDB1-WDFY1 as an E3 Ubiquitin Ligase Complex Involved in Initiation of Lysophagy.” *Cell Reports* 40: 111349.

De Tito, S., et al. 2024. “ATG9A and ARFIP2 Cooperate to Regulate PI4P Levels for Lysosomal Repair.” *bioRxiv*. https://doi.org/10.1101/2024.07.23.604321.

Trajkovic, K., C. Hsu, S. Chiantia, et al. 2008. “Ceramide Triggers Budding of Exosome Vesicles Into Multivesicular Endosomes.” *Science* 319: 1244–1247. https://doi.org/10.1126/science.1153124.

Udeochu, J. C., S. Amin, Y. Huang, et al. 2023. “Tau Activation of Microglial cGAS-IFN Reduces MEF2C-mediated Cognitive Resilience.” *Nature Neuroscience* 26: 737–750. https://doi.org/10.1038/s41593-023-01315-6.

Vergarajauregui, S., J. A. Martina, and R. Puertollano. 2009. “Identification of the Penta-EF-Hand Protein ALG-2 as a Ca2+-Dependent Interactor of Mucolipin-1.” *Journal of Biological Chemistry* 284: 36357–36366. https://doi.org/10.1074/jbc.M109.047241.

Vietri, M., M. Radulovic, and H. Stenmark. 2020a. “The Many Functions of ESCRTs.” *Nature Reviews Molecular Cell Biology* 21: 25–42. https://doi.org/10.1038/s41580-019-0177-4.

Vietri, M., M. Radulovic, and H. Stenmark. 2020b. “The Many Functions of ESCRTs.” *Nature Reviews Molecular Cell Biology* 21: 25–42. https://doi.org/10.1038/s41580-019-0177-4.

Wang, F., et al. 2023b. “ATG5 Provides Host Protection Acting as a Switch in the atg8ylation Cascade Between Autophagy and Secretion.” *Developmental Cell* 58: e868. https://doi.org/10.1016/j.devcel.2023.03.014.

Wang, F., R. Gómez-Sintes, and P. Boya. 2018. “Lysosomal Membrane Permeabilization and Cell Death.” *Traffic* 19: 918–931.

Wang, X., P. Xu, A. Bentley-DeSousa, et al. 2025. “The Bridge-Like Lipid Transport Protein VPS13C/PARK23 Mediates ER–Lysosome Contacts Following Lysosome Damage.” *Nature Cell Biology* ahead of print. https://doi.org/10.1038/s41556-025-01653-6.

Wang, Y., et al. 2023a. “TECPR1 Provides E3-Ligase Like Activity to the ATG5-ATG12 Complex to Conjugate LC3/ATG8 to Damaged Lysosomes.” *bioRxiv*. https://doi.org/10.1101/2023.06.24.546289.

Willett, R., J. A. Martina, J. P. Zewe, R. Wills, G. R. V. Hammond, and R. Puertollano. 2017. “TFEB Regulates Lysosomal Positioning by Modulating TMEM55B Expression and JIP4 Recruitment to Lysosomes.” *Nature Communications* 8: 1580. https://doi.org/10.1038/s41467-017-01871-z.

Wong, A. O., M. Marthi, A. Haag, I. A. Owusu, C. E. Wobus, and J. A. Swanson. 2022. “Macrophage Inflammatory State Influences Susceptibility to Lysosomal Damage.” *Journal of Leukocyte Biology* 111: 629–639. https://doi.org/10.1002/jlb.3a0520-325rr.

Xie, X., G. Ma, X. Li, J. Zhao, Z. Zhao, and J. Zeng. 2023. “Activation of Innate Immune cGAS-Sting Pathway Contributes to Alzheimer's Pathogenesis in 5× FAD Mice.” *Nature Aging* 3: 202–212.

Xu, Y., P. Zhou, S. Cheng, et al. 2019. “A Bacterial Effector Reveals the V-ATPase-ATG16L1 Axis That Initiates Xenophagy.” *Cell* 178: e520.

Xun, J., Z. Zhang, B. Lv, et al. 2024. “A Conserved Ion Channel Function of STING Mediates Noncanonical Autophagy and Cell Death.” *EMBO Reports* 25: 544–569. https://doi.org/10.1038/s44319-023-00045-x.

Yang, H., and J. X. Tan. 2023. “Lysosomal Quality Control: Molecular Mechanisms and Therapeutic Implications.” *Trends in Cell Biology* 33: 749–764. https://doi.org/10.1016/j.tcb.2023.01.001.

Yang, P., C. Mathieu, R. M. Kolaitis, et al. 2020. “G3BP1 Is a Tunable Switch That Triggers Phase Separation to Assemble Stress Granules.” *Cell* 181: e328. https://doi.org/10.1016/j.cell.2020.03.046.

Yim, W. W. Y., H. Yamamoto, and N. Mizushima. 2022. “Annexins A1 and A2 Are Recruited to Larger Lysosomal Injuries Independently of ESCRTs to Promote Repair.” *FEBS Letters* 596: 991–1003.

Yong, J., J. E. Villalta, N. Vu, et al. 2024. “Impairment of Lipid Homeostasis Causes Lysosomal Accumulation of Endogenous Protein Aggregates Through ESCRT Disruption.” *eLife* 12: RP86194. https://doi.org/10.7554/eLife.86194.

Young, J. C. 2010. “Mechanisms of the Hsp70 Chaperone System.” *Biochemistry and Cell Biology* 88: 291–300. https://doi.org/10.1139/o09-175.

Yu, L., C. K. McPhee, and L. Zheng, et al. 2010. “Termination of Autophagy and Reformation of Lysosomes Regulated by mTOR.” *Nature* 465: 942–946.

Zhang, W., X. Yang, L. Chen, et al. 2021. “A Conserved Ubiquitin- and ESCRT-Dependent Pathway Internalizes Human Lysosomal Membrane Proteins for Degradation.” *PLoS Biology* 19: e3001361. https://doi.org/10.1371/journal.pbio.3001361.

Zhen, Y., M. Radulovic, M. Vietri, and H. Stenmark. 2021. “Sealing Holes in Cellular Membranes.” *EMBO Journal* 40: e106922. https://doi.org/10.15252/embj.2020106922.

Zhu, L., J. R. Jorgensen, M. Li, Y.-S. Chuang, and S. D. Emr. 2017. “ESCRTs Function Directly on the Lysosome Membrane to Downregulate Ubiquitinated Lysosomal Membrane Proteins.” *eLife* 6: e26403.