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Review

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mTOR and lysosome repair: from adaptive response to neurodegenerative vulnerability

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Abstract: Dysregulation of mechanistic target of rapamycin (mTOR) signaling is a common feature of neurodegenerative disease, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), frontotemporal dementia (FTD), and amyotrophic lateral sclerosis (ALS). Under physiological conditions, transient lysosomal rupture triggers a protective response: mTOR activity is temporarily suppressed, autophagy is activated, and lysosomal repair programs re-establish cellular homeostasis. However, chronic mTOR hyperactivation—driven by genetic variants, aging-related signaling changes, or metabolic imbalance—can impair this adaptive lysosomal stress response. Persistent mTOR activity impairs lysosomal repair efficiency and autophagic clearance, promoting the accumulation of damaged organelles and protein aggregates. Building on this compromised degradative capacity, mTOR dysregulation may not directly initiate disease, but instead sensitizes cells to proteotoxic and lysosomal stress, markedly increasing vulnerability. This review integrates findings that support mTOR-associated lysosomal vulnerability as a convergent mechanism in post-mitotic cells and discusses its implications for cellular resilience, disease susceptibility, and therapeutic intervention.

Key words: mTOR; Lysosomes; Lysosomal damage response; Neurodegenerative diseases

1 Introduction

Post-mitotic cells, particularly neurons, rely on precise regulation of lysosomal function to maintain cellular homeostasis. Lysosomes not only mediate the degradation and recycling of cellular components but also serve as critical signaling hubs, integrating nutrient and stress cues (Savini et al., 2019; Ballabio and Bonifacino, 2020). Increasing evidence indicates that disruptions in lysosomal integrity and repair can contribute to the pathogenesis of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (Koh et al., 2019; Nixon and Rubinsztein, 2024). mTOR coordinates autophagy induction, protein synthesis, and lysosomal biogenesis, allowing cells to adapt to fluctuations in stress and nutrient status. Under conditions of chronic mTOR hyperactivation—driven by genetic variants,

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aging, or metabolic stress—lysosomal repair is impaired, leading to organelle dysfunction, protein aggregation, and increased cellular vulnerability (Ilha et al., 2018; Panwar et al., 2023; Tan and Finkel, 2023; Meyer and Kravic, 2024). Importantly, mTOR dysregulation is unlikely to act as a primary initiator of neurodegenerative disease. Instead, we propose that under conditions of lysosomal stress or rupture, impaired mTOR-mediated repair programs may lower the cellular threshold for injury and accelerate proteotoxicity. This framework provides a mechanistic basis for understanding how mTOR contributes to disease susceptibility and progression.

In this review, we summarize current knowledge of lysosomal damage responses, regulation of mTOR signaling at the lysosome, and downstream pathways that coordinate membrane repair. We integrate evidence from neurodegenerative disease and discuss how mTOR-dependent lysosomal adaptation may shape disease progression. Finally, we highlight mTOR-targeted interventions and explore the potential relevance of these findings to lysosomal damage responses, acknowledging that the connection requires validation.

2 Lysosomes and Lysosomal Damage Response

2.1 Lysosomes: Central Hubs for Cellular Homeostasis

Lysosomes, the essential degradative organelles of eukaryotic cells, represent the terminal compartment of multiple endocytic and autophagic pathways, and maintain cellular metabolic balance. These organelles harbor a broad repertoire of acid hydrolases that degrade both endogenous and exogenous macromolecules. By fusing with autophagosomes, lysosomes facilitate clearance and recycling of damaged organelles and misfolded proteins (Savini et al., 2019; Ballabio and Bonifacino, 2020). Consequently, functional integrity of lysosomes is essential for cellular homeostasis and energy metabolism.

2.2 Types of Lysosomal Damage and Recognition Mechanisms

The integrity of the lysosomal membrane is indispensable for maintaining its degradative capacity and cellular homeostasis. Structural compromise to the lysosomal membrane leads to leakage of luminal contents, including hydrolases and calcium ions, which can induce cellular stress or apoptosis (Wang et al., 2018). Lysosomal membrane damage can arise from diverse sources (Fig. 1a), including endogenous oxidative stress, Fenton reactions (Kurz et al., 2007; Ghosh et al., 2011), proteolytic enzymes, and alterations in membrane lipid composition (Le Joncour et al., 2019; Ebner et al., 2025), as well as exogenous mechanical damage caused by particulate matter (e.g., uric acid crystals) and pathogens (Duewell and Latz, 2013). In neurodegenerative disease, aggregated proteins—including α-synuclein, huntingtin, and Aβ —can accumulate within lysosomes via endocytosis, inducing metabolic overload and subsequent membrane rupture (Nixon and Rubinsztein, 2024). Accordingly, cells have evolved multiple sensing mechanisms to promptly detect injury and initiate repair or clearance programs. Due to a range of upstream stressors, lysosomal membrane rupture represents a common downstream event (Zhu et al., 2020; ScottOri et al., 2025). Following membrane injury, cells rely primarily on two upstream mechanisms for damage recognition: rapid Ca^{2+} influx–dependent signaling and galectin-mediated detection of exposed luminal glycans on ruptured endo-lysosomal membranes (Hoyer et al., 2022; Chen et al., 2024).

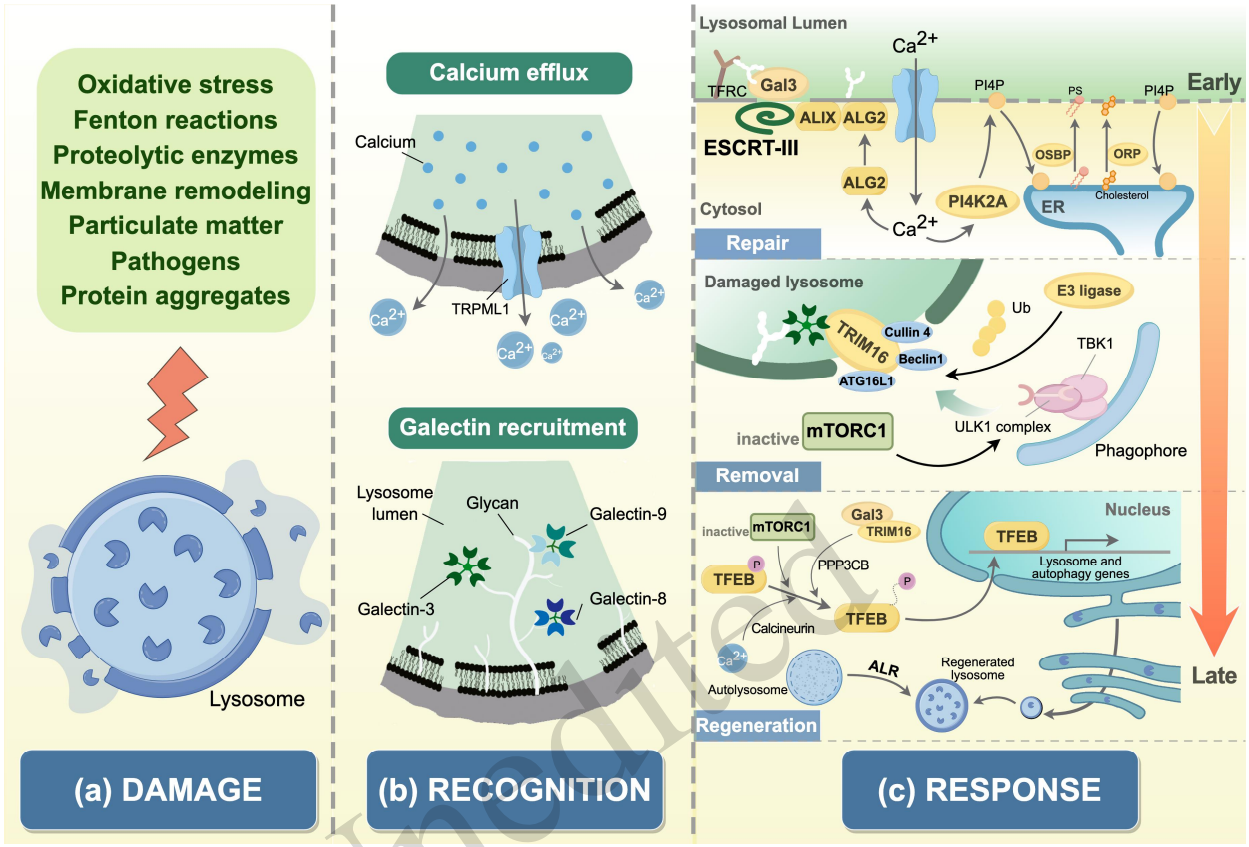

Fig. 1 Lysosomal damage – triggers, sensing mechanisms, and adaptive responses. (a) Damage: Lysosomal membrane integrity is compromised by diverse endogenous and exogenous stressors. (b) Recognition: Top – Lysosomal Ca^{2+} leaks into the cytosol upon membrane injury; activation of TRPML1 enhances this efflux, giving a transient local Ca^{2+} surge as an early damage signal. Bottom – Galectin proteins (Gal3, Gal8, Gal9) rapidly bind exposed intraluminal glycans on damaged lysosomes and relay damage signals to downstream hubs. (c) Response: Repair (top panel) – Ca^{2+} efflux triggers ALG2 and PI4K2A; ALG2 recruits ALIX (with Gal3) to assemble ESCRT-III (CHMP4A/B) at lesion sites for membrane resealing, while PI4K2A generates PI4P to recruit OSBP/ORP lipid-transfer proteins from the ER for membrane replenishment. Removal (middle panel) – Gal3/TRIM16 complex recruits autophagy receptors to damaged lysosomes; ubiquitination enhances recognition, while mTORC1 inactivation initiates ULK1-mediated autophagosome formation and TBK1 further promotes receptor function, targeting autophagosomes to the damaged organelles. Regeneration (bottom panel) – mTORC1 inactivation, Ca^{2+}–calcineurin signaling and Gal3–TRIM16–PPP3CB axis promote TFEB dephosphorylation and nuclear translocation, driving lysosomal biogenesis. Meanwhile, the AIR (autolysosome-independent recycling) pathway regenerates proto-lysosomes from autolysosomal content. Created by figdraw.com (ID: YOYYS1df4e).

Ca^{2+} signaling serves as one of the earliest indicators of lysosomal membrane rupture (Meyer and Kravic, 2024; Fig. 1b, top panel). Lysosomes act as major intracellular Ca^{2+} reservoirs, with luminal Ca^{2+} concentrations far exceeding those in the cytosol (Christensen et al., 2002; Zajac et al., 2024). Increased membrane permeability triggers rapid calcium efflux through channels such as TRPML1, subsequently activating calcineurin and promoting TFEB dephosphorylation. Notably, localized Ca^{2+} leakage also induces LC3 lipidation, a prerequisite for full TFEB activation during the lysosomal damage response (Nakamura et al., 2020; Galione et al., 2021). Together, this signaling cascade enhances autophagy and lysosomal biogenesis, promoting cellular repair (Lloyd-Evans and Waller-Evans, 2020; Medina, 2021).

Members of the Galectin family achieve spatially precise recognition of lysosomal damage by binding to exposed β-galactoside residues on ruptured membranes (Barondes et al., 1994; Papadopoulos and Meyer, 2017; Fig. 1b, bottom panel). Galectin-3 (Gal3), Galectin-8 (Gal8), and Galectin-9 (Gal9) rapidly accumulate on

ruptured lysosomal membranes, orchestrating distinct signaling events: Gal3 activates ESCRT-III-mediated membrane repair and mTOR regulation; Gal8 modulates mTORC1 activity via Rag GTPase regulation; and Gal9 participates in mTOR and ULK1 signaling through AMPK (Thurston et al., 2012; Chauhan et al., 2016; Jia, 2018; Shariq et al., 2024). Collectively, these mechanisms constitute an integrated lysosomal damage-sensing network, providing critical safeguards for cellular responses to injury.

2.3 Fundamental Pathways of Lysosomal Damage Response

The integrity of the lysosomal membrane is essential for maintaining intracellular homeostasis. Upon lysosomal membrane damage, cells rapidly activate a highly coordinated response system comprising three core mechanisms: repair, removal, and regeneration, which together form the foundational framework for the lysosomal damage response (Jia et al., 2020b, 2020c; Meyer and Kravic, 2024; Shariq et al., 2024).

2.3.1 Repair

During the early phase of damage, cells prioritize membrane repair to salvage compromised lysosomes (Fig. 1c, top panel). Upon membrane rupture, Ca^{2+} efflux activates ALG-2, which recruits ESCRT complex components (e.g., ALIX, CHMP4A/B) to drive membrane invagination and sealing and restore structural integrity (Henne et al., 2013; Papadopoulos and Meyer, 2017; Radulovic et al., 2018; Skowyra et al., 2018). Gal3, a key damage sensor, recognizes exposed glycosylated structures and directs ESCRT assembly at injury sites (Radulovic et al., 2018; Jia et al., 2020b, 2020c). Assisted by its chaperone transferrin receptor (TFRC), Gal3 rapidly accumulates at damaged membrane sites and recruits ALG-2 interacting protein X (ALIX) to injury loci. ALIX subsequently orchestrates the assembly of ESCRT-III core subunits CHMP4A/B to activate ESCRT-mediated membrane-repair mechanisms, preserving lysosomal membrane integrity (Henne et al., 2013; Radulovic et al., 2018; Skowyra et al., 2018; Jia et al., 2020b, 2020c). Additionally, cells engage the membrane lipid metabolism in repair processes. For example, PI4K2A-generated PI4P promotes endoplasmic reticulum-lysosome membrane contacts, facilitating lipid transport mediated by OSBP/ORP family proteins (Tan and Finkel, 2022). Concurrently, ceramide produced by sphingomyelinase facilitates membrane-curvature changes, stabilizing and invaginating damaged regions (Meyer and Kravic, 2024).

2.3.2 Removal

When repair alone fails to restore lysosomal integrity, cells switch to selective autophagy (lysophagy) to eliminate damaged lysosomes (Skowyra et al., 2018; Jia et al., 2020b, 2020c; Shariq et al., 2024; Fig. 1c, middle panel). Gal3, continuing a key role in this phase, collaborates with Tripartite Motif-Containing 16 (TRIM16) to recruit autophagy receptors (e.g., OPTN, TAX1BP1), bridging damaged sites to the autophagy machinery (Meyer and Kravic, 2024). TRIM16, the 16th member of the TRIM protein family, plays a dual role in the autophagic process as both a receptor and a regulator (Mandell et al., 2020). It not only interacts with Gal3 in an ULK1-dependent manner to recognize signals of lysosomal damage, but also mediates the ubiquitination of multiple autophagy factors: TRIM16 has an E3 ligase domain, and its self-ubiquitination in complex with another E3-Ub ligase, Cullin 4A, induces the ubiquitination of key autophagy regulators ULK1 and Beclin1. TRIM16 can also form a complex with them to stabilize these factors and trigger autophagy (Chauhan et al., 2016; Fraiberg and Elazar, 2016; Christ et al., 2017; Kumar et al., 2017). Ubiquitination of damaged membrane proteins and signaling tags mediated by E3 ligases (e.g., UBE2QL1) further aid in target recognition. Then, facilitated by the loss of mTORC1-mediated inhibitory phosphorylation, the ULK1 complex (including ATG13, FIP200, and ATG101) is activated to initiate phagophore formation. TRIM16 also interacts with ATG16L1 to facilitate LC3 lipidation and autophagosome biogenesis (Chauhan et al., 2016), while TBK1 phosphorylates autophagy receptors, enhancing their affinity for LC3 and promoting targeting of autophagosomal membranes to ubiquitin-marked damaged lysosomes for sequestration and clearance (Hoyer et al., 2022; Meyer and Kravic, 2024).

2.3.3 Regeneration

Post-clearance regeneration primarily relies on transcription factors such as TFEB (Fig. 1c, bottom panel). Under normal conditions, mTORC1 phosphorylates and retains TFEB in the cytoplasm, whereas lysosomal damage suppresses mTORC1 activity and allows its release. Alternatively, TFEB can be directly activated by mTOR-independent pathways. For instance, lysosomal Ca^{2+} release stimulates calcineurin, a Ca^{2+}-dependent phosphatase, to dephosphorylate TFEB and promote its nuclear translocation (Medina et al., 2015; Martina and Puertollano, 2018). Similarly, Gal3-recruited TRIM16 complex incorporates Protein Phosphatase 3 Catalytic Subunit Beta (PPP3CB), which directly activates TFEB and promotes its nuclear translocation (Chauhan et al., 2016; Shariq et al., 2024). Damage signals induce TFEB dephosphorylation and nuclear translocation, initiating CLEAR (Coordinated Lysosomal Expression and Regulation) element-driven gene-expression programs to upregulate lysosomal hydrolases, membrane proteins, and autophagy-related factors (Barondes et al., 1994; Lloyd-Evans and Waller-Evans, 2020; Zhu et al., 2020). This activation is primarily triggered by lysosomal membrane damage and the consequent Ca^{2+} release. When extensive autophagic activity depletes existing lysosomes, the autophagic lysosome reformation (ALR) pathway is initiated to regenerate proto-lysosomes and then restore lysosomal homeostasis (Nanayakkara et al., 2022). This process involves KIF5B-driven membrane tubule elongation and clathrin/dynamin 2-mediated membrane scission to generate proto-lysosomes. ATG2 and ORP proteins also participate in lipid transfer to replenish membrane structure and function (Nanayakkara et al., 2022; Meyer and Kravic, 2024).

The lysosomal damage response exemplifies cellular adaptability to endogenous stress. Through the temporally coordinated interplay of membrane repair, selective clearance, and biogenesis, cells maintain lysosomal homeostasis and functional integrity. This framework provides critical insights into lysosomal dysfunction mechanisms underlying various diseases.

3 Overview of the mTOR Pathway

The mechanistic target of rapamycin (mTOR) is an evolutionarily conserved serine/threonine protein kinase belonging to the PI3K-related kinase (PIKK) family. It functions as a central signaling hub regulating cell growth, metabolism, and stress responses. mTOR operates through two distinct complexes—mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2)—which integrate and relay various cellular signals (Saxton and Sabatini, 2017; Panwar et al., 2023).

3.1 Composition and Functions of mTORC1 and mTORC2

mTORC1 is composed of the catalytic subunit mTOR, the scaffold protein Raptor, and the stabilizing protein mLST8; it dynamically associates with PRAS40 and DEPTOR to modulate its kinase activity and substrate specificity (Fig. 2a). Cryo-electron microscopy studies have revealed that mTORC1 forms a stable dimer with Raptor as its core, and exhibits high sensitivity to rapamycin. Key functions of mTORC1 include: 1) Promoting protein synthesis via phosphorylation of S6K1 and 4EBP1; 2) Driving lipid and nucleotide synthesis through SREBP and CAD; 3) Suppressing autophagy and lysosomal biogenesis under nutrient-rich conditions by inhibiting ULK1 and TFEB. Through these processes, mTORC1 acts as a master regulator of nutrient sensing and metabolic reprogramming (Yip et al., 2010; Aylett et al., 2016).

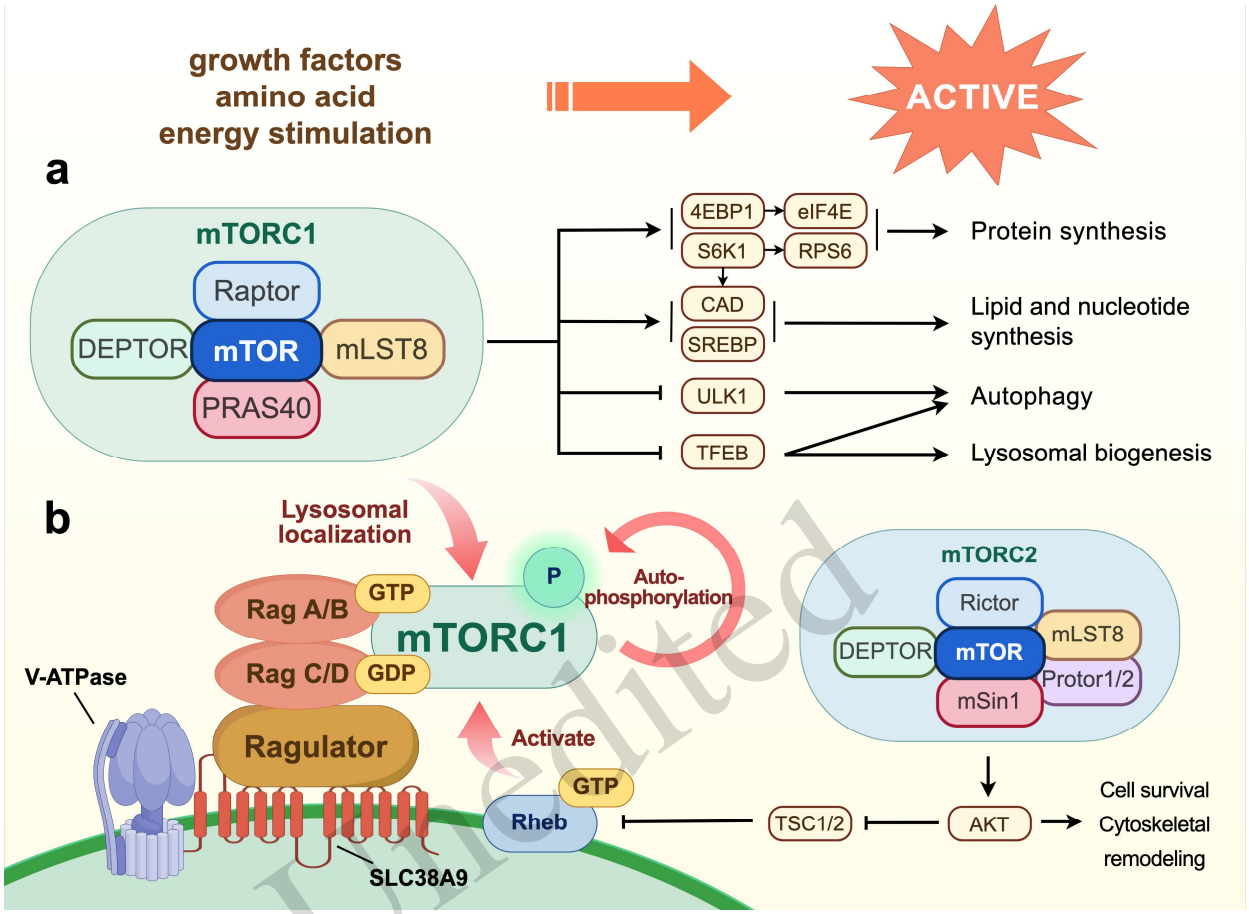

Fig. 2 mTORC1 and mTORC2: structure, regulation, and core functions. (a) Complex composition and major functions: The two major mTOR complexes are mTORC1 (mTOR, Raptor, mLST8, PRAS40, DEPTOR) and mTORC2 (mTOR, Rictor, mSin1, mLST8, Protor1/2). mTORC1 functions as a metabolic hub promoting protein synthesis (via S6K1 and 4EBP1 → RPS6 and eIF4E), nucleotide synthesis (via CAD), and lipid biosynthesis (via SREBP), and suppresses autophagy/lysosome biogenesis (via ULK1 and TFEB phosphorylation). mTORC2 regulates cell survival and cytoskeleton via Akt-phosphorylation and can inhibit TSC1/2 to activate Rheb and thereby drive mTORC1 activity. (b) Lysosomal recruitment and activation of mTORC1: At the lysosomal membrane, a multiprotein hub (V-ATPase, SLC38A9, Ragulator, and Rag GTPases RagA/B and RagC/D) mediates mTORC1 localisation. Under growth-factor, amino-acid, or energy stimulation, the Rag GTPases adopt an active configuration, recruiting mTORC1 to the lysosome where proximity to Rheb allows allosteric activation, autophosphorylation, and subsequent downstream substrate phosphorylation. Created by figdraw.com (ID: AUYSI9aa69).

In contrast, mTORC2 consists of mTOR, Rictor, mSin1, mLST8, and Protor1/2, and can also associate with the inhibitory subunit DEPTOR. It primarily governs cell survival and cytoskeletal remodeling through phosphorylation of targets such as Akt (Ser473) and PKC. Activated Akt further phosphorylates and inhibits the TSC1/2 complex, thereby relieving its suppression of Rheb and promoting mTORC1 activity, establishing regulatory crosstalk between the two complexes (Panwar et al., 2023; Marafie et al., 2024). mTORC2 activity depends on phosphatidylinositol-(3,4,5)-trisphosphate (PIP3) generated by PI3K and the membrane localization mediated by the PH domain of mSin1(Yip et al., 2010; Aylett et al., 2016).

3.2 Lysosomal Localization and Activation Mechanism of mTORC1

Activation of mTORC1 is heavily dependent on its lysosomal localization (Fig. 2b). Under nutrient-replete or energy-stimulated conditions, Rag GTPases—heterodimers of RagA/B and RagC/D—adopt an active conformation (RagA/B-GTP, RagC/D-GDP), recruiting mTORC1 to the lysosomal membrane (Sancak et al.,

2008; Kim et al., 2008; Takahara et al., 2020; Gollwitzer et al., 2022). This process is scaffolded by the GATOR-KICSTOR supercomplex, whose intricate molecular architecture and role in nutrient sensing have been further elucidated by recent high-resolution structural studies (Valenstein et al., 2025; Lupton et al., 2026). Once positioned on the lysosome, mTORC1 encounters Rheb, a small GTPase in its GTP-bound state, which directly activates mTORC1 through conformational modulation of its kinase domain (Long et al., 2005; Jia, 2018). Rheb activity is negatively regulated by the TSC1/2 complex, where TSC2 acts as a GTPase-activating protein (GAP) that converts Rheb-GTP to Rheb-GDP. Various stress signals (e.g., energy deprivation, hypoxia, DNA damage) activate TSC1/2 complex and promote its lysosomal localization, thereby inhibiting Rheb and terminating mTORC1 signaling (Jozwiak et al., 2005; Yang et al., 2020; Napolitano et al., 2022).

4 Regulation of mTORC1 Inactivation Upon Lysosomal Damage

The activity of mTORC1 is tightly coupled to its localization on the lysosomal surface, and structural integrity of a lysosome—as a signaling hub—is essential for accurate mTOR signal transduction (Carosi et al., 2021; Napolitano et al., 2022). Despite extensive investigation into the functional interplay between mTOR and lysosomes in metabolic and growth control, the regulatory mechanisms of the mTOR pathway under lysosomal damage conditions remain insufficiently characterized.

Recent studies have shown that lysosomal membrane permeabilization (LMP) causes mTORC1 to dissociate from lysosomal membranes, leading to its functional inactivation (Carosi et al., 2021; Napolitano et al., 2022; Shariq et al., 2024). Yet, the precise damage-associated signals mediating this process and the downstream pathways dictating cellular fate remain poorly understood. Emerging evidence emphasizes a mechanistic link between lysosomal damage sensing and mTORC1 regulation. Lysosomal dysfunction often coincides with mTOR dysregulation in various pathological contexts, including neurodegenerative disease (Nixon, 2013; Querfurth and Lee, 2021; Jiao et al., 2022; Ondaro et al., 2022), muscular atrophy (Abokyi et al., 2023; Lu et al., 2025), and tumor microenvironments (Johnson and Tee, 2017; Mossmann et al., 2018; Murugan, 2019). Therefore, elucidating the interplay between lysosomal damage and mTOR dysregulation remains a central challenge in disease.

Lysosomes serve as the principal platforms for mTORC1 activation, with their membrane integrity being essential for signaling stability. Upon lysosomal membrane permeabilization, two hallmark events ensue: rapid Ca^{2+} efflux into the cytosol and recruitment of galectin proteins—most notably Galectin-3, -8, and -9—through their binding to exposed luminal glycans. These damage-sensing pathways collectively lead to a third consequence: dissociation of mTORC1 from the lysosomal surface.

4.1 The Ca^{2+}-CASM-mTOR axis

Ca^{2+} signaling serves not only as an early indicator of lysosomal injury but also as a direct modulator of the mTORC1 pathway through multiple molecular mechanisms (Fig. 3a). Under physiological conditions, the activity of lysosomal membrane-localized mTORC1 depends on nutrient signaling mediated by the Rag GTPase family (Gollwitzer et al., 2022).

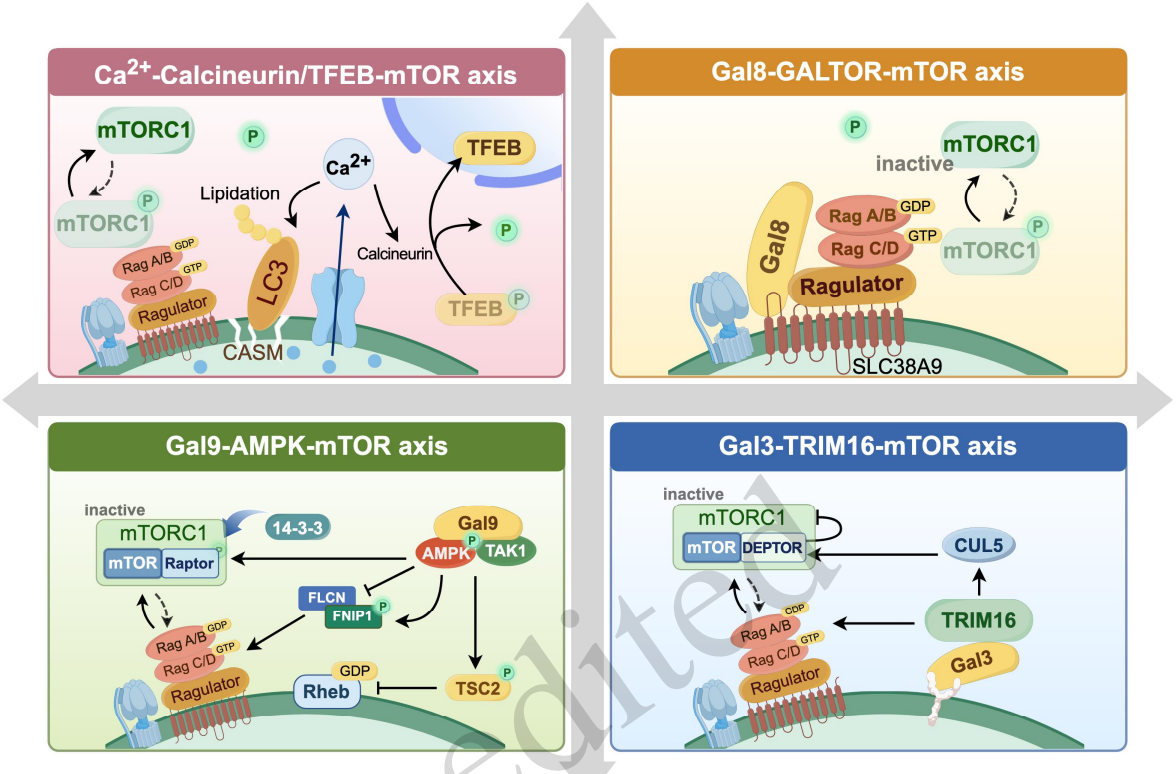

Fig. 3 mTORC1 inactivation upon lysosomal damage. Four mechanistic axes by which lysosomal membrane damage signals converge to inactivate mTORC1 . This causes its dissociation from lysosomes and loss of its kinase activity, thus initiating downstream repair responses. (a) Ca^{2+}–calcineurin/TFEB–mTOR axis: Lysosomal membrane injury causes a rapid cytosolic Ca^{2+} surge, which triggers lipidation of ATG8 (e.g., LC3) on the damaged membrane via the CASM pathway. This membrane remodelling disrupts Rag-GTPase–mTORC1 interaction, preventing mTORC1 anchoring and activation. (b) Gal8–GALTOR–mTOR axis: Gal8 accumulates on damaged lysosomal membranes and interfaces with the Ragulator–Rag–SLC38A9 (GALTOR) complex; these interactions competitively interfere with Rag-mediated mTORC1 anchoring, promoting lysosomal dissociation and inactivation of mTORC1. (c) Gal9 – AMPK – mTOR axis: Lysosomal damage recruits Gal9, which activates TAK1→AMPK; AMPK suppresses mTORC1 via (i) phosphorylation of Raptor (enhancing 14-3-3 binding), (ii) phosphorylation of TSC2 (reducing Rheb-GTP loading), and (iii) phosphorylation of FNIP1 (maintaining RagC/D in GTP bound state and disrupting mTORC1 lysosomal localisation). (d) Gal3–TRIM16–mTOR axis: The Gal3–TRIM16 complex stabilises DEPTOR via interaction with the cullin ubiquitin ligase system, thereby inhibiting mTORC1 kinase activity; concurrently, it interacts with RagB/D GTPases to impair mTORC1 localisation to the lysosome. Created by figdraw.com (ID: YYAWUb613d).

Under injury conditions, however, the efflux of Ca^{2+} from compromised lysosomes disrupts mTORC1 membrane localization and diminishes its kinase activity (Li et al., 2016; Nakamura et al., 2020; Galione et al., 2021; Medina, 2021). Ca^{2+} leakage triggers a rapid, non-canonical autophagy process termed CASM (conjugation of ATG8 to single membranes). In this pathway, cytosolic Ca^{2+} elevation following lysosomal rupture promotes lipidation of ATG8 family proteins (e.g., LC3) directly onto the damaged lysosomal membrane, instead of forming a traditional autophagosome. This atypical membrane anchoring of LC3 reshapes the lysosomal surface structure, destabilizing the interaction between Rag GTPases and mTORC1, and consequently impairing mTORC1's recruitment and activity (Nakamura et al., 2020; Meyer and Kravic, 2024). Together, these events illustrate how Ca^{2+} leakage couples lysosomal membrane remodeling to suppression of mTORC1 signaling.

4.2 The Gal8-GALTOR-mTOR Axis

Galectin-8 (Gal8), a member of the LGALS family, is rapidly recruited from the cytoplasm to damaged lysosomal membranes via exposed glycan chains; there it exerts its inhibitory effect on mTOR through direct interactions with the Ragulator-Rag SLC38A9 system (Fig. 3b). Under physiological conditions, the Ragulator-Rag complex anchors mTORC1 to the lysosomal surface. Upon membrane damage, however, Gal8 binding to Ragulator disrupts this anchoring, resulting in mTORC1 inhibition and dissociation from the lysosomal membrane (Jia, 2018; Acharya and Demetriades, 2024). It is worth noting that the Ragulator-Rag complex is capable of interacting with both mTORC1 and Gal8. When the lysosome is damaged, the interaction between SLC38A9 and Gal8 strengthens the association of Gal8 with the Ragulator-Rag complex, modulating the subcellular localization and activation status of mTORC1 (Jia, 2018). In summary, Gal8 binds to the Ragulator-Rag SLC38A9 system within GALTOR to compete with mTORC1, and then displaces it from the lysosomal membrane, leading to its inactivation.

4.3 The Gal9-AMPK-mTOR Axis

In addition to Gal8, the exposed glycans recruit Galectin (Gal9) to the damaged lysosomal membrane, where it binds to Transforming growth factor-β-activated kinase 1 (TAK1, also known as MAP3K7, an upstream kinase of AMPK) phosphorylating threonine 172 (T172) of AMPKα (Protein kinase AMP-activated catalytic subunit alpha 2, PRKAA2), thus activating AMPK (Jia, 2018; Jia et al., 2019, 2020a; Fig. 3c).

Due to the critical roles of AMPK and mTOR in cellular energy metabolism, growth, proliferation, and autophagy, the overlap in their pathways has long been a focus of investigation. AMPK inhibits mTORC1 kinase activity by phosphorylating TSC2, thereby repressing Rheb activity. In parallel, AMPK directly phosphorylates regulatory-associated protein of mTOR (Raptor) at Ser72 and Ser792, facilitating the binding of 14-3-3 protein to Raptor, which impairs the ability of mTORC1 to recruit and phosphorylate downstream substrates (Shaw et al., 2004; Gwinn et al., 2008; Kim et al., 2011). Additionally, AMPK phosphorylates several serine residues within folliculin-interacting protein 1 (FNIP1), inhibiting the function of the FLCN-FNIP1 complex, which acts as a GAP for RagC/D (Shaw et al., 2004; Gwinn et al., 2008; Garcia and Shaw, 2017; Malik et al., 2023). In summary, Gal9 functions as a molecular conduit that transduces lysosomal damage signals into activation of AMPK, thereby modulating the mTOR signaling cascade (Jia, 2018; Jia et al., 2019, 2020a).

4.4 The Gal3-TRIM16-mTOR Axis

Galectin-3 (Gal3) also plays a pivotal role in the response to lysosomal damage (Fig. 3d). As a key damage-associated signaling molecule, Gal3 differs from other LGALS family members (e.g., Gal8 and Gal9) in its broader functional spectrum and its regulation of multiple, distinct downstream pathways. As described above, Gal3 participates not only in the initial repair phase following lysosomal damage, but also in later stages of autophagic clearance and lysosomal regeneration, orchestrating the full continuum of lysosomal damage responses (Jia et al., 2020c). In addition to mediating ESCRT-dependent lysosomal repair and TRIM16-driven autophagy, Gal3 further modulates mTOR activity through direct interaction with TRIM16 (Chauhan et al., 2016; Fraiberg and Elazar, 2016; Christ et al., 2017; Kumar et al., 2017). Upon persistent lysosomal damage, Gal3 forms a complex with TRIM16, which in turn associates with a complex containing DEPTOR (DEP domain-containing mTOR-interacting protein) and cullin 5 (CUL5, an E3-Ub ligase), to modulate the stability of DEPTOR, a negative regulator of mTORC1. Stabilization of DEPTOR under lysosomal stress strengthens its inhibitory potency, thereby suppressing mTORC1 activity. Moreover, TRIM16 interacts with RagB/D GTPases, suppressing lysosomal localization of mTORC1 (Okumura et al., 2016; Catena and Fanciulli, 2017; Kumar et al., 2017; Takahara et al., 2020).

These mechanisms share common upstream triggers—lysosomal membrane rupture leading to Ca^{2+} efflux and exposure of lumenal glycans—and ultimately converge on suppression of mTOR signaling. However, the

temporal hierarchy and interdependence among these pathways remain poorly defined, as direct comparative or causality-oriented studies are still lacking.

5 From mTOR Inhibition to the Lysosomal Damage Response

5.1 ULK1: Activation of Autophagy and Lysosomal Clearance

mTORC1 plays a pivotal regulatory role in lysosomal clearance by directly controlling the activation and functional assembly of ULK1 complex (comprising ATG13, FIP200, and ATG101). Under nutrient-replete conditions, mTORC1 phosphorylates ULK1 (Ser757) and ATG13 (Ser258), suppressing the activity of ULK1 complex and blocking its assembly and capacity to recruit autophagosomal precursor membranes. This dual phosphorylation mechanism ensures autophagy suppression during favorable metabolic states (Alers et al., 2012; Walker and Ktistakis, 2020). The inhibition depends on mTORC1 anchoring to the lysosomal membrane, where its kinase activity phosphorylates the ULK1 complex and blocks recruitment of downstream autophagy proteins (e.g., ATG14, Beclin-1). Consequently, ULK1-mediated steps in autophagosome biogenesis, including membrane nucleation and elongation, are stringently suppressed, preventing unnecessary autophagy and maintaining cellular homeostasis (Saxton and Sabatini, 2017; Jia et al., 2019).

When lysosomal membrane integrity is compromised, damage signals trigger mTORC1 dissociation from lysosomes and subsequent inactivation (Alers et al., 2012; Saxton and Sabatini, 2017; Shariq et al., 2024). The loss of mTORC1 activity leads to dephosphorylation and structural remodeling of the ULK1 complex: dephosphorylation of ULK1 at Ser757 relieves spatial inhibition, enabling autophosphorylation within its activation loop (Thr180). This activation enables ULK1 to phosphorylate ATG13 and FIP200, leading to the assembly of a functional autophagy-initiation complex. Activated ULK1 drives autophagosome dynamics through several mechanisms. First, it phosphorylates AMBRA1 (the activating molecule in Beclin1-regulated autophagy protein 1) to recruit the class III PI3K complex (VPS34-Beclin1-ATG14), which generates PI3P to promote isolation-membrane nucleation. It is noteworthy that recent evidence identifies lysosomal PI3P as a key rheostat that also acts upstream to destabilize Rag-mTORC1 signaling under stress (Picot et al., 2026). The second mechanism occurs when activated ULK1 facilitates membrane expansion via lipid transfer by ATG2 from the endoplasmic reticulum and coordinates with the ATG9 vesicle system to elongate the double-membrane structure. It also recruits the ATG conjugation system (ATG16L1-ATG5-ATG12) through PI3P-dependent binding of WIPI2, thereby mediating LC3 lipidation to modify the phagophore. The fourth mechanism is enabling selective recognition of damaged lysosomes via autophagy receptors that bridge ubiquitin tags on injured lysosomes and LC3 on autophagosomal membranes. Ultimately, mature autophagosomes fuse with lysosomes to form autolysosomes, in which lysosomal hydrolases degrade damaged components. This process not only eliminates dysfunctional lysosomes but also prevents leakage of cytotoxic enzymes (e.g., cathepsins), thereby blocking apoptosis cascades; this highlights the dual protective role of ULK1-mediated selective autophagy in lysosomal quality control (Jung et al., 2009; Walker and Ktistakis, 2020; Meyer and Kravic, 2024).

5.2 TFEB: Promoting Lysosomal Regeneration and Functional Restoration

Under physiological conditions, mTORC1 tightly regulates TFEB localization and activity through dynamic phosphorylation. When intracellular amino acids are abundant, mTORC1 forms an active complex with the Rag GTPase heterodimer (RagA/B-RagC/D) on lysosomal membranes. This complex directly phosphorylates TFEB at Ser211, which masks its nuclear localization signal (NLS) and exposes its nuclear export signal (NES), thereby promoting its binding to the 14-3-3 chaperone protein. This interaction generates steric hindrance, forcing TFEB to remain sequestered in the cytoplasm (Roczniak-Ferguson et al., 2012; Martina et al., 2012; Cui et al., 2023). Additionally, mTORC1 cooperatively phosphorylates TFEB at Ser142 and Ser122 residues as auxiliary sites, further suppressing its transcriptional activity through a multi-layered

regulatory network (Napolitano et al., 2018; Martina and Puertollano, 2018). Upon lysosomal damage, mTORC1 dissociates from the lysosomal membranes and becomes inactivated. This inactivation leads to dephosphorylation of TFEB at Ser211, releasing it from 14-3-3 binding and unmasking its NLS, which enables rapid nuclear translocation (Shariq et al., 2024). Concurrently, damage-specific signals amplify TFEB activation via the calcium-calcineurin pathway: leaked Ca^{2+} binds calmodulin to activate calcineurin, which directly dephosphorylates TFEB at Ser211 and Ser142, accelerating its nuclear import (Medina et al., 2015; Martina and Puertollano, 2018). Once translocated into the nucleus and activated, TFEB orchestrates lysosome biogenesis by globally coordinating the transcription of lysosomal genes; these genes are involved in synthesis, assembly, and functional maturation. At the transcriptional level, TFEB binds CLEAR elements in promoters to activate genes encoding lysosomal hydrolases (e.g., cathepsin B/D, α-glucosidase GAA), lysosomal membrane proteins (LAMP1/2, V-ATPase subunits), and autophagy-related molecules (SQSTM1/p62, LC3) (Sardiello and Ballabio, 2009; Sardiello et al., 2009; Palmieri et al., 2011; Napolitano and Ballabio, 2016).

As it drives lysosome biogenesis, TFEB simultaneously establishes a self-reinforcing regulatory circuit by upregulating members of the ATG8 family (Jia et al., 2022; Shariq et al., 2024). Following nuclear translocation, TFEB activates transcription of ATG family genes to assemble the ATG16L1/ATG5/ATG12 complex, which promotes conjugation of ATG8 family proteins (e.g., MAP1LC3s and GABARAPs) to phosphatidylethanolamine (PE) for canonical autophagosome formation—a process known as the ATG8 conjugation machinery (Lystad and Simonsen, 2019; Iriondo et al., 2023). In non-canonical autophagy, ATG8 can also conjugate to phosphatidylserine (PS) on single membranes, a process termed CASM (Conjugation of ATG8 to Single Membranes) (Durgan and Florey, 2021, 2022; Meyer and Kravic, 2024). ATG8ylation exerts dual effects: (1) it disrupts mTOR-dependent TFEB phosphorylation via the GABARAP-FLCN/FNIP1/2-TFEB axis, and (2) activates TRPML1, a lysosomal Ca^{2+} channel, promoting Ca^{2+} efflux and subsequent activation of the calcineurin isoform PPP3BCB, which in turn directly dephosphorylates TFEB at Ser211 and Ser142 (Nakamura et al., 2020; Jia et al., 2022; Shariq et al., 2024). Collectively, the TFEB–ATG8ylation–TRPML1–Ca^{2+}–TFEB axis constitutes a self-reinforcing positive feedback loop via the dual mechanisms described above. Furthermore, ATG8ylation of damaged lysosomes mediates lysosomal membrane repair via non-canonical microautophagy, preventing further leakage of cytotoxic contents (Meyer and Kravic, 2024). This self-regulatory mechanism not only amplifies lysosomal regeneration signaling but also spatiotemporally couples lysosome biogenesis with autophagic clearance. Specifically ATG8-dependent membrane repair predominates at early damage stages to preserve lysosomal integrity, while ATG8-mediated autophagy removes irreparably damaged lysosomes, creating space for TFEB-driven nascent lysosomes. This dynamic equilibrium ensures quality control of the lysosomal pool, thus providing a dual protective safeguard for cells to cope with persistent stress.

6 Disease Relevance of mTOR Signaling in Lysosomal Rupture Regulation

Recent studies suggest that mTOR signaling becomes aberrantly activated in several neurodegenerative diseases (Querfurth and Lee, 2021), including Alzheimer's disease (AD) (Davoody et al., 2023), Parkinson's disease (PD) (Fernández-Santiago et al., 2019), Huntington's disease (HD) (Stavrides et al., 2025), frontotemporal dementia (FTD), and amyotrophic lateral sclerosis (ALS) (Shao et al., 2020). Although the precise mechanisms by which genetic or functional variants within the mTOR pathway influence disease onset and progression remain incompletely understood (Olney et al., 2017; Fernández-Santiago et al., 2019), sustained mTOR dysregulation is increasingly recognized as a critical modifier of disease progression rather than a direct initiator.

Lysosomal membrane rupture represents a ubiquitous cellular stress response observed across diverse neurodegenerative disorders (Udayar et al., 2022). Such rupture events trigger a coordinated defensive program encompassing calcium efflux, recruitment of Galectin family proteins to damaged membranes, activation of

CASM and the GALTOR complex, and calcineurin-mediated signaling. Together, these pathways determine the balance between protein aggregate clearance, lysosomal repair and regeneration, and ultimate cell-viability decisions.

Persistent activation of mTORC1 may interfere with the cell's intrinsic lysosomal self-repair and re-formation programs, thereby promoting protein aggregation, compromising lysosomal recovery, and accelerating degenerative processes. Elucidating the disease relevance of lysosomal rupture–mediated mTOR signaling may therefore yield valuable insights into disease mechanisms and uncover novel therapeutic strategies.

6.1 Aggregate-Induced Lysosomal Rupture and mTOR Dysregulation in Neurodegenerative Disease

Across neurodegenerative diseases (NDDs) such as PD, AD, and ALS, accumulation of misfolded proteins—including α-synuclein, β-amyloid, tau, and TDP-43—perturbs lysosomal membrane integrity and promotes rupture, leading to proton leakage and a consequent loss of enzymatic activity (Koh et al., 2019; Chou et al., 2025). These aggregate-induced lysosomal injuries disrupt proteostasis and trigger maladaptive stress signaling, primarily by means of the mTOR pathway.

As a central hub governing lysosomal function and proteostasis, mTORC1 becomes aberrantly hyperactivated in multiple NDDs, coupling protein aggregation to impaired autophagy and lysosomal collapse (Ghavami et al., 2014; Querfurth and Lee, 2021). In AD, both postmortem brain tissue and experimental models consistently reveal sustained activation of the mTOR pathway. Aβ peptides can activate mTOR signaling by phosphorylating PRAS40, an inhibitory component of mTORC1, which establishes a self-reinforcing loop that accelerates amyloid pathology and neuronal damage (Davoody et al., 2023). In PD, pathogenic α-synuclein directly binds to and destabilizes the TSC1–TSC2 complex, resulting in aberrant mTORC1 activation, excessive protein synthesis, and dopaminergic neuronal degeneration (Khan et al., 2023). Genetic data further support mTOR as a disease modifier: interaction between the SNCA SNP rs356219 and mTOR pathway genes (RPTOR, RPS6KA2) significantly influences PD onset age (Fernández-Santiago et al., 2019; Coleman and Martin, 2022), suggesting that mTOR signaling regulates α-synuclein–linked pathology rather than directly causing disease.

In ALS, a highly complex neurodegenerative disorder, dysregulated mTOR activity contributes to disease pathophysiology (Nogueira-Machado et al., 2025). Analyses of human ALS spinal-cord tissue suggest overactivation of the Akt/mTOR signaling axis—marked by increased p-Akt and p-S6 alongside decreased p27Kip1 and BCL-2—linking this pathway to motor-neuron vulnerability (Jung et al., 2025). The stress-granule protein STAU1 is overabundant in ALS, FTD, SCA2, HD, and AD, where it enhances mTOR translation and hyperactivation, thereby impairing autophagic flux (Paul et al., 2021; Zhao et al., 2024). Notably, ANXA11-associated mechanisms also support a link between mTOR dysregulation and ALS. In an ALS mouse model harboring the ANXA11-P36R mutation, persistent mTORC1 hyperactivation and aggregate accumulation were detected in both motor neurons and skeletal muscles, though the underlying mechanism remains unclear (Liu et al., 2025). Consistently, recent work from our laboratory demonstrates that *Anxa11* knockout indirectly promotes mTOR recruitment to the lysosomal membrane, activating downstream signaling pathways and providing an additional mechanism by which ANXA11 may contribute to ALS risk (Tang et al., unpublished data). Finally, phosphorylation of Rab7 by ALS/FTD-linked TBK1 (E696K) mutants relieves Rab7-mediated suppression of amino-acid-dependent mTORC1 activation, further connecting lysosomal dysfunction to mTOR dysregulation (Talaia et al., 2024). Collectively, these findings highlight the lysosome as a critical platform for efficient mTORC1 activation in ALS.

Although some models suggest that transient mTOR activation may offer short-term neuroprotection (Zhang et al., 2011; Saxena et al., 2013), chronic mTOR hyperactivation generally worsens disease progression by reducing neuronal resilience to proteotoxic and lysosomal stress. Indeed, rapamycin and related mTOR inhibitors have been tested in randomized controlled trials for ALS (Mandrioli et al., 2018).

Collectively, these findings highlight that mTOR dysregulation disrupts neuronal proteostasis and

metabolic adaptability, diminishing cellular resilience to lysosomal injury and accelerating neurodegenerative progression (Ghavami et al., 2014; Ondaro et al., 2022).

6.2 Chronic mTORC1 Activation Impairs Lysosomal Repair and Exacerbates Proteotoxic Stress

Under pathological conditions, sustained mTORC1 activation not only suppresses autophagy initiation by inhibiting ULK1 but also blocks TFEB/TFE3 activation and lysosomal gene transcription (Martina et al., 2012). Consequently, damaged lysosomes accumulate and proteotoxic stress intensifies. This cascade—lysosomal injury → impaired response → persistent damage—converges on aberrant mTOR activation as a pivotal node, forming a self-perpetuating vicious cycle that accelerates neurodegeneration.

Inhibition of mTOR with drugs such as rapamycin and its analogs has shown therapeutic promise in multiple NDD models, reducing aggregate burden and improving behavioral outcomes. For example, IGF1R overexpression drives mTOR pathway dysregulation, thereby inhibiting autophagy; while inhibiting the IGF1R-mTOR axis counteracts the toxic effects of these astrocytes on motor neurons in SOD1 mutant mice (Table 1; Granatiero et al., 2021; Khan et al., 2023; Kumar et al., 2023; Lanza et al., 2025; Yajuan Wu et al., 2025; Yanqing Wu et al., 2025).

Table 1 Representative preclinical studies targeting mTOR in neurodegenerative disorders.

Disease	Model	Treatment	Results	Reference
AD	APP/PS1 transgenic mouse	PF-04691502 (1 mg/kg)	● Enhanced cognitive performance and significantly reduced insoluble Aβ accumulation in the brain.	(Lanza et al., 2025)
	P301S tau transgenic mice	(-)-Epicatechin (50 mg/kg for 2 months)	● Rescued cognitive deficits in spatial learning and memory. ● Significantly reduced insoluble total Tau and phosphorylated Tau accumulation in the brain. ● Reversed synapse loss, neuronal loss, and alleviated neuroinflammation.	(Wu et al., 2025a)
	APP/PS1 transgenic mouse of	DNLA (20 and 40 mg/kg/day for 5 months)	● Significantly delayed the onset of learning and memory impairment. ● Enhanced Aβ degradation and protein levels of intracellular $A\beta_{1-40}$ and $A\beta_{1-42}$ in the hippocampus. ● Alleviated senescence of hippocampal neurons by promoting lysosomal acidification and improving autophagic flux.	(Wu et al., 2025b)
PD	Human iPSC DA neurons with GBA1 heterozygote mutations (GBA1/PD−DA)	mTOR catalytic inhibitor INK128/TAK228	● Prevented the increase in phosphorylated α-syn (p−S129) levels and α-syn aggregation. ● reduced LC3−II and p62 levels.	(Kumar et al., 2023)
	α-Syn PFF mouse (intrastriatal injection) α-syn transgenic Drosophila	Rapamycin (6 mg/kg via intraperitoneal injection or fed in the diet)	● Rescued dopamine neuron loss, motor deficits, and increased lifespan. ● Reduced pathologic p−S129 α-syn immunoreactivity.	(Khan et al., 2023)
ALS	iPSA with $SOD1^{G93A}$ mutations cultured with motor neurons	Torin1 (250 nM)	● Rescued the macroautophagy defect in the astrocytes. ● Decreased the pathological cell proliferation of the astrocytes. ● Reduced astrocyte reactivity, shown by lower levels of GFAP protein and a panel of key reactive astrocyte mRNA markers.	(Granatiero et al., 2021)

AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; APP/PS1, amyloid precursor protein/presenilin 1; iPSC, induced pluripotent stem cells; DA, dopaminergic; α-syn, α-synuclein; PFF, pre-formed fibrils; iPSA, iPSC-derived astrocyte; DNLA, *Dendrobium nobile* Lindl. alkaloids; Aβ, amyloid-β; p-S129, phosphorylated at serine 129; LC3-II, microtubule-associated protein 1 light chain 3B-II; p62, sequestosome 1; GFAP, glial fibrillary acidic protein.

From the mechanistic perspective proposed in this review, the therapeutic benefit of mTOR inhibition likely extends beyond autophagy activation to include restoration or reprogramming of lysosomal damage-sensing and repair mechanisms. This framework provides an integrated explanation of how mTOR-targeted therapies stabilize lysosomal integrity and slow neurodegenerative progression, even when mTOR dysregulation is not the primary disease cause.

7 Discussion and Perspectives

mTOR signaling integrates nutrient availability, cellular stress, and organelle function, and its dysregulation is widely observed across neurodegenerative and neuromuscular diseases. Yet, how mTOR responds to specific forms of intracellular damage—particularly lysosomal injury—remains insufficiently understood. In this review, we focused on the molecular mechanisms linking mTOR activity to lysosomal stress responses, a process that forms one component of the broader proteostasis network essential for cellular survival.

Over the past decade, studies have revealed that lysosomal integrity is monitored by multiple upstream sensors, including galectins, calcium flux, ESCRT components, and membrane-repair machinery. These pathways collectively modulate mTORC1 localization and activity, thereby influencing autophagy initiation, lysosomal biogenesis, and protein turnover. Although these mechanisms have mainly been characterized in cell-based systems, they provide a conceptual framework for understanding how cells adapt mTOR signaling during proteotoxic or mechanical stress.

Protein aggregation and impaired proteostasis are hallmark features of many neurodegenerative disorders. In these diseases, mutations in SNCA, STAU1, SOD1, or other proteostasis regulators disrupt autophagy–lysosome coupling and can result in sustained mTORC1 activity. However, it is important to emphasize that these diseases are not solely lysosomal disorders; mitochondrial dysfunction, ER stress, inflammation, and RNA-binding protein dysregulation also contribute to pathology. Therefore, mTOR-mediated lysosomal damage responses likely represent one component within a multi-layered pathological landscape, rather than a unifying mechanism.

Within this context, we propose a testable hypothesis: mTOR dysregulation in neurodegenerative diseases may impair lysosomal damage response and reduce the cell's capacity to manage aggregate-induced stress, thereby influencing disease progression.

This hypothesis does not assign lysosomal damage repair a central or exclusive role, but rather positions it as a potential regulatory node shaped by mTOR activity alongside other stress pathways. Future studies integrating live-cell imaging, lysosomal membrane-repair assays, and disease models will be crucial for determining whether impaired mTOR-dependent lysosomal repair contributes directly to aggregate accumulation or acts as a secondary amplifier of cellular stress.

Therapeutically, broad mTOR inhibition remains challenging due to its pleiotropic effects on metabolism, translation, and synaptic function. Precision strategies that selectively modulate the lysosome-associated arm of mTOR signaling—such as fine-tuning the mTOR–TFEB–Rag GTPase axis or stabilizing lysosomal membranes—may offer a more targeted approach to restoring proteostasis. Such interventions may complement existing therapies aimed at reducing protein aggregation or enhancing autophagic flux.

In conclusion, the interplay between mTOR signaling and lysosomal stress responses provides a promising framework for understanding cellular resilience in neurodegenerative disease. By reframing lysosomal repair as part of an integrated proteostasis network rather than a singular determinant of pathology, future research can better dissect how mTOR contributes to disease vulnerability and identify more precise therapeutic targets.

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Author contributions

Liyang MA contributed to Writing – original draft. Tianzhen LIU contributed to Content expansion and Writing – review and editing. Jingyi ZHOU, Wen TANG, Jinjie ZHONG, and Ge BAI contributed to Writing – review and editing, with Ge Bai providing critical input and insightful questions that strengthened the manuscript. Guoping PENG and Zhen ZHONG contributed to Conceptualization, Supervision, and Project administration. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Liyang MA, Tianzhen LIU, Jingyi ZHOU, Wen TANG, Jinjie ZHONG, Ge BAI, Guoping PENG, and Zhen ZHONG declare that they have no conflicts of interest.

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

Declaration on the use of generative AI tools

During the preparation of this work, the authors used Gemini and Grammarly in order to refine the linguistic expression and perform grammatical polishing of the manuscript. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

References

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

Acharya, A., Demetriades, C., 2024. mTORC1 activity licenses its own release from the lysosomal surface. *Molecular Cell*, 84(22):4385-4400.e7. https://doi.org/10.1016/j.molcel.2024.10.008

Alers, S., Löffler, A.S., Wesselborg, S., *et al.*, 2012. Role of AMPK-mTOR-Ulk1/2 in the Regulation of Autophagy: Cross Talk, Shortcuts, and Feedbacks. *Molecular and Cellular Biology*, 32(1):2–11. https://doi.org/10.1128/MCB.06159-11

Aylett, C.H.S., Sauer, E., Imseng, S., *et al.*, 2016. Architecture of human mTOR complex 1. *Science*, 351(6268):48–52. https://doi.org/10.1126/science.aaa3870

Ballabio, A., Bonifacino, J.S., 2020. Lysosomes as dynamic regulators of cell and organismal homeostasis. *Nature Reviews. Molecular Cell Biology*, 21(2):101–118. https://doi.org/10.1038/s41580-019-0185-4

Barondes, S.H., Castronovo, V., Cooper, D.N.W., *et al.*, 1994. Galectins: A family of animal β-galactoside-binding lectins. *Cell*, 76(4):597–598. https://doi.org/10.1016/0092-8674(94)90498-7

Carosi, J.M., Fourrier, C., Bensalem, J., *et al.*, 2021. The mTOR–lysosome axis at the centre of ageing. *FEBS Open Bio*, 12(4):739–757. https://doi.org/10.1002/2211-5463.13347

Catena, V., Fanciulli, M., 2017. Deptor: not only a mTOR inhibitor. *Journal of experimental & clinical cancer research: CR*, 36(1):12. https://doi.org/10.1186/s13046-016-0484-y

Chauhan, S., Kumar, S., Jain, A., *et al.*, 2016. TRIMs and Galectins Globally Cooperate and TRIM16 and Galectin-3 Co-direct Autophagy in Endomembrane Damage Homeostasis. *Developmental Cell*, 39(1):13–27. https://doi.org/10.1016/j.devcel.2016.08.003

Chen, W., Motsinger, M.M., Li, J., *et al.*, 2024. Ca2+-sensor ALG-2 engages ESCRTs to enhance lysosomal membrane resilience to osmotic stress. *Proceedings of the National Academy of Sciences*, 121(22):e2318412121. https://doi.org/10.1073/pnas.2318412121

Chou, C.-C., Vest, R., Prado, M.A., *et al.*, 2025. Proteostasis and lysosomal repair deficits in transdifferentiated neurons of Alzheimer's disease. *Nature Cell Biology*, 27(4):619–632. https://doi.org/10.1038/s41556-025-01623-y

Christ, L., Raiborg, C., Wenzel, E.M., *et al.*, 2017. Cellular Functions and Molecular Mechanisms of the ESCRT Membrane-Scission Machinery. *Trends in Biochemical Sciences*, 42(1):42–56. https://doi.org/10.1016/j.tibs.2016.08.016

Christensen, K.A., Myers, J.T., Swanson, J.A., 2002. pH-dependent regulation of lysosomal calcium in macrophages. *Journal of Cell Science*, 115(3):599–607. https://doi.org/10.1242/jcs.115.3.599

Coleman, C., Martin, I., 2022. Unraveling Parkinson's Disease Neurodegeneration: Does Aging Hold the Clues? *Journal of Parkinson's Disease*, 12(8):2321–2338. https://doi.org/10.3233/JPD-223363

Cui, Z., Napolitano, G., de Araujo, M.E.G., *et al.*, 2023. Structure of the lysosomal mTORC1–TFEB–Rag–Ragulator megacomplex. *Nature*, 614(7948):572–579. https://doi.org/10.1038/s41586-022-05652-7

Davoody, S., Asgari Taei, A., Khodabakhsh, P., *et al.*, 2023. mTOR signaling and Alzheimer's disease: What we know and where we are? *CNS Neuroscience & Therapeutics*, 30(4):e14463. https://doi.org/10.1111/cns.14463

Duewell, P., Latz, E., 2013. Assessment and quantification of crystal-induced lysosomal damage. *Methods in Molecular Biology (Clifton, N.J.)*, 1040:19–27. https://doi.org/10.1007/978-1-62703-523-1_3

Durgan, J., Florey, O., 2021. A new flavor of cellular Atg8-family protein lipidation – alternative conjugation to phosphatidylserine during CASM. *Autophagy*, 17(9):2642–2644. https://doi.org/10.1080/15548627.2021.1947730

Durgan, J., Florey, O., 2022. Many roads lead to CASM: Diverse stimuli of noncanonical autophagy share a unifying molecular mechanism. *Science Advances*, 8(43):eabo1274. https://doi.org/10.1126/sciadv.abo1274

Ebner, M., Fröhlich, F., Haucke, V., 2025. Mechanisms and functions of lysosomal lipid homeostasis. *Cell Chemical Biology*, 32(3):392–407. https://doi.org/10.1016/j.chembiol.2025.02.003

Fernández-Santiago, R., Martín-Flores, N., Antonelli, F., *et al.*, 2019. SNCA and mTOR Pathway Single Nucleotide Polymorphisms Interact to Modulate the Age at Onset of Parkinson's Disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, 34(9):1333–1344. https://doi.org/10.1002/mds.27770

Fraiberg, M., Elazar, Z., 2016. A TRIM16-Galactin3 Complex Mediates Autophagy of Damaged Endomembranes. *Developmental Cell*, 39(1):1–2. https://doi.org/10.1016/j.devcel.2016.09.025

Galione, A., Davis, L.C., Morgan, A.J., 2021. A cellular protection racket: How lysosomal Ca2+ fluxes prevent kidney injury. *Cell Calcium*, 93:102328. https://doi.org/10.1016/j.ceca.2020.102328

Garcia, D., Shaw, R.J., 2017. AMPK: Mechanisms of Cellular Energy Sensing and Restoration of Metabolic Balance. *Molecular Cell*, 66(6):789–800. https://doi.org/10.1016/j.molcel.2017.05.032

Ghavami, S., Shojaei, S., Yeganeh, B., *et al.*, 2014. Autophagy and apoptosis dysfunction in neurodegenerative disorders. *Progress in Neurobiology*, 112:24–49. https://doi.org/10.1016/j.pneurobio.2013.10.004

Ghosh, M., Carlsson, F., Laskar, A., *et al.*, 2011. Lysosomal membrane permeabilization causes oxidative stress and ferritin induction in macrophages. *FEBS letters*, 585(4):623–629. https://doi.org/10.1016/j.febslet.2010.12.043

Gollwitzer, P., Grützmacher, N., Wilhelm, S., *et al.*, 2022. A Rag GTPase dimer code defines the regulation of mTORC1 by amino acids. *Nature Cell Biology*, 24(9):1394–1406. https://doi.org/10.1038/s41556-022-00976-y

Granatiero, V., Sayles, N.M., Savino, A.M., *et al.*, 2021. Modulation of the IGF1R-MTOR pathway attenuates motor neuron toxicity of human ALS SOD1G93A astrocytes. *Autophagy*, 17(12):4029–4042. https://doi.org/10.1080/15548627.2021.1899682

Gwinn, D.M., Shackelford, D.B., Egan, D.F., *et al.*, 2008. AMPK phosphorylation of raptor mediates a metabolic checkpoint. *Molecular Cell*, 30(2):214–226. https://doi.org/10.1016/j.molcel.2008.03.003

Henne, W.M., Stenmark, H., Emr, S.D., 2013. Molecular mechanisms of the membrane sculpting ESCRT pathway. *Cold Spring Harbor Perspectives in Biology*, 5(9):a016766. https://doi.org/10.1101/cshperspect.a016766

Hoyer, M.J., Swarup, S., Wade Harper, J., 2022. Mechanisms controlling selective elimination of damaged lysosomes. *Current Opinion in Physiology*, 29:100590. https://doi.org/10.1016/j.cophys.2022.100590

Ilha, J., do Espírito-Santo, C.C., de Freitas, G.R., 2018. mTOR Signaling Pathway and Protein Synthesis: From Training to Aging and Muscle Autophagy. *Advances in Experimental Medicine and Biology*, 1088:139–151. https://doi.org/10.1007/978-981-13-1435-3_7

Iriondo, M.N., Etxaniz, A., Varela, Y.R., *et al.*, 2023. Effect of ATG12–ATG5-ATG16L1 autophagy E3-like complex on the ability of LC3/GABARAP proteins to induce vesicle tethering and fusion. *Cellular and Molecular Life Sciences: CMLS*, 80(2):56. https://doi.org/10.1007/s00018-023-04704-z

Jia, J., 2018. Galectins Control mTOR in Response to Endomembrane Damage. *Molecular Cell*, 70(1):120–135.

Jia, J., Abudu, Y.P., Claude-Taupin, A., *et al.*, 2019. Galectins control MTOR and AMPK in response to lysosomal damage to induce autophagy. *Autophagy*, 15(1):169–171. https://doi.org/10.1080/15548627.2018.1505155

Jia, J., Bissa, B., Brecht, L., *et al.*, 2020a. AMPK is activated during lysosomal damage via a galectin-ubiquitin signal transduction system. *AUTOPHAGY*, 16(8):1550–1552. https://doi.org/10.1080/15548627.2020.1788890

Jia, J., Claude-Taupin, A., Gu, Y., *et al.*, 2020b. MERIT, a cellular system coordinating lysosomal repair, removal and replacement. *Autophagy*, 16(8):1539–1541. https://doi.org/10.1080/15548627.2020.1779451

Jia, J., Claude-Taupin, A., Gu, Y., *et al.*, 2020c. Galectin-3 Coordinates a Cellular System for Lysosomal Repair and Removal. *Developmental Cell*, 52(1):69-87.e8. https://doi.org/10.1016/j.devcel.2019.10.025

Jia, J., Wang, F., Bhujabal, Z., *et al.*, 2022. Stress granules and mTOR are regulated by membrane atg8ylation during lysosomal damage. *Journal of Cell Biology*, 221(11):e202207091. https://doi.org/10.1083/jcb.202207091

Jiao, F., Zhou, B., Meng, L., 2022. The regulatory mechanism and therapeutic potential of transcription factor EB in neurodegenerative diseases. *CNS Neuroscience & Therapeutics*, 29(1):37–59. https://doi.org/10.1111/cns.13985

Johnson, C.E., Tee, A.R., 2017. Exploiting cancer vulnerabilities: mTOR, autophagy, and homeostatic imbalance. *Essays in*

Biochemistry, 61(6):699–710. https://doi.org/10.1042/EBC20170056

Jozwiak, J., Jozwiak, S., Grzela, T., *et al.*, 2005. Positive and negative regulation of TSC2 activity and its effects on downstream effectors of the mTOR pathway. *Neuromolecular Medicine*, 7(4):287–296. https://doi.org/10.1385/NMM:7:4:287

Jung, C.H., Jun, C.B., Ro, S.-H., *et al.*, 2009. ULK-Atg13-FIP200 Complexes Mediate mTOR Signaling to the Autophagy Machinery. *Molecular Biology of the Cell*, 20(7):1992–2003. https://doi.org/10.1091/mbc.E08-12-1249

Jung Y., Tognoni C.M., Aksut O., *et al.*, 2025. Overactivation of Akt/Mtor Signaling and Decreased Expression of P27 Kip1 Associates with Motor Neuron Neurodegeneration in the Spinal Cord of Als Patients. Social Science Research Network, Rochester, NY, https://papers.ssrn.com/abstract=5180196. https://doi.org/10.2139/ssrn.5180196

Khan, M.R., Yin, X., Kang, S.-U., *et al.*, 2023. Enhanced mTORC1 signaling and protein synthesis in pathologic α-synuclein cellular and animal models of Parkinson's disease. *Science Translational Medicine*, 15(724):eadd0499. https://doi.org/10.1126/scitranslmed.add0499

Kim, E., Goraksha-Hicks, P., Li, L., *et al.*, 2008. Regulation of TORC1 by Rag GTPases in nutrient response. *Nature Cell Biology*, 10(8):935–945. https://doi.org/10.1038/ncb1753

Kim, J., Kundu, M., Viollet, B., *et al.*, 2011. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nature Cell Biology*, 13(2):132–141. https://doi.org/10.1038/ncb2152

Koh, J.-Y., Kim, H.N., Hwang, J.J., *et al.*, 2019. Lysosomal dysfunction in proteinopathic neurodegenerative disorders: possible therapeutic roles of cAMP and zinc. *Molecular Brain*, 12(1):18. https://doi.org/10.1186/s13041-019-0439-2

Kumar, M., Srikanth, M.P., Deleidi, M., *et al.*, 2023. Acid ceramidase involved in pathogenic cascade leading to accumulation of α-synuclein in iPSC model of GBA1-associated Parkinson's disease. *Human Molecular Genetics*, 32(11):1888–1900. https://doi.org/10.1093/hmg/ddad025

Kumar, S., Chauhan, S., Jain, A., *et al.*, 2017. Galectins and TRIMs directly interact and orchestrate autophagic response to endomembrane damage. *Autophagy*, 13(6):1086–1087. https://doi.org/10.1080/15548627.2017.1307487

Kurz, T., Terman, A., Brunk, U.T., 2007. Autophagy, ageing and apoptosis: the role of oxidative stress and lysosomal iron. *Archives of Biochemistry and Biophysics*, 462(2):220–230. https://doi.org/10.1016/j.abb.2007.01.013

Lanza, M., Basilotta, R., Caccamo, A., *et al.*, 2025. PF-04691502, a PI3K/mTOR Dual Inhibitor, Ameliorates AD-like Pathology in a Mouse Model of AD. *Cells*, 14(18):1474. https://doi.org/10.3390/cells14181474

Le Joncour, V., Filppu, P., Hyvönen, M., *et al.*, 2019. Vulnerability of invasive glioblastoma cells to lysosomal membrane destabilization. *EMBO molecular medicine*, 11(6):e9034. https://doi.org/10.15252/emmm.201809034

Li, R.-J., Xu, J., Fu, C., *et al.*, 2016. Regulation of mTORC1 by lysosomal calcium and calmodulin. *eLife*, 5:e19360. https://doi.org/10.7554/eLife.19360

Liu, Q., Sun, Y., He, B., *et al.*, 2025. Gain-of-function ANXA11 mutation cause late-onset ALS with aberrant protein aggregation, neuroinflammation and autophagy impairment. *Acta Neuropathologica Communications*, 13(1):2. https://doi.org/10.1186/s40478-024-01919-4

Lloyd-Evans, E., Waller-Evans, H., 2020. Lysosomal Ca2+ Homeostasis and Signaling in Health and Disease. *Cold Spring Harbor Perspectives in Biology*, 12(6):a035311. https://doi.org/10.1101/cshperspect.a035311

Long, X., Lin, Y., Ortiz-Vega, S., *et al.*, 2005. Rheb Binds and Regulates the mTOR Kinase. *Current Biology*, 15(8):702–713. https://doi.org/10.1016/j.cub.2005.02.053

Lu, Y., Tian, J., Deng, J., *et al.*, 2025. Metabolic and proteomic profiles provide insights on mechanism of late onset Pompe disease. *Molecular Genetics and Metabolism*, 144(3):109045. https://doi.org/10.1016/j.ymgme.2025.109045

Lupton, C.J., Bayly-Jones, C., Dong, S., *et al.*, 2026. Structure of the lysosomal KICSTOR-GATOR1-SAMTOR nutrient-sensing supercomplex. *Cell*, 189(4):1185-1200.e28. https://doi.org/10.1016/j.cell.2025.12.005

Lystad, A.H., Simonsen, A., 2019. Mechanisms and Pathophysiological Roles of the ATG8 Conjugation Machinery. *Cells*, 8(9):973. https://doi.org/10.3390/cells8090973

Malik, N., Ferreira, B.I., Hollstein, P.E., *et al.*, 2023. Induction of lysosomal and mitochondrial biogenesis by AMPK phosphorylation of FNIP1. *Science (New York, N.Y.)*, 380(6642):eabj5559. https://doi.org/10.1126/science.abj5559

Mandell, M.A., Saha, B., Thompson, T.A., 2020. The Tripartite Nexus: Autophagy, Cancer, and Tripartite Motif-Containing Protein Family Members. *Frontiers in Pharmacology*, 11:308. https://doi.org/10.3389/fphar.2020.00308

Mandrioli, J., D'Amico, R., Zucchi, E., *et al.*, 2018. Rapamycin treatment for amyotrophic lateral sclerosis: Protocol for a phase II randomized, double-blind, placebo-controlled, multicenter, clinical trial (RAP-ALS trial). *Medicine*, 97(24):e11119. https://doi.org/10.1097/MD.0000000000011119

Marafie, S.K., Al-Mulla, F., Abubaker, J., 2024. mTOR: Its Critical Role in Metabolic Diseases, Cancer, and the Aging Process. *International Journal of Molecular Sciences*, 25(11):6141. https://doi.org/10.3390/ijms25116141

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

Martina, J.A., Puertollano, R., 2018. Protein phosphatase 2A stimulates activation of TFEB and TFE3 transcription factors in response to oxidative stress. *The Journal of Biological Chemistry*, 293(32):12525–12534.

https://doi.org/10.1074/jbc.RA118.003471
Medina, D.L., 2021. Lysosomal calcium and autophagy. *International Review of Cell and Molecular Biology*, 362:141–170. https://doi.org/10.1016/bs.ircmb.2021.03.002
Medina, D.L., Di Paola, S., Peluso, I., *et al.*, 2015. Lysosomal calcium signaling regulates autophagy via calcineurin and TFEB. *Nature cell biology*, 17(3):288–299. https://doi.org/10.1038/ncb3114
Meyer, H., Kravic, B., 2024. The Endo-Lysosomal Damage Response. *Annual Review of Biochemistry*, 93(1):367–387. https://doi.org/10.1146/annurev-biochem-030222-102505
Mossmann, D., Park, S., Hall, M.N., 2018. mTOR signalling and cellular metabolism are mutual determinants in cancer. *Nature Reviews. Cancer*, 18(12):744–757. https://doi.org/10.1038/s41568-018-0074-8
Murugan, A.K., 2019. mTOR: Role in cancer, metastasis and drug resistance. *Seminars in Cancer Biology*, 59:92–111. https://doi.org/10.1016/j.semcancer.2019.07.003
Nakamura, S., Shigeyama, S., Minami, S., *et al.*, 2020. LC3 lipidation is essential for TFEB activation during the lysosomal damage response to kidney injury. *Nature Cell Biology*, 22(10):1252–1263. https://doi.org/10.1038/s41556-020-00583-9
Nanayakkara, R., Gurung, R., Rodgers, S.J., *et al.*, 2022. Autophagic lysosome reformation in health and disease. *Autophagy*, 19(5):1378–1395. https://doi.org/10.1080/15548627.2022.2128019
Napolitano, G., Ballabio, A., 2016. TFEB at a glance. *Journal of Cell Science*, 129(13):2475–2481. https://doi.org/10.1242/jcs.146365
Napolitano, G., Esposito, A., Choi, H., *et al.*, 2018. mTOR-dependent phosphorylation controls TFEB nuclear export. *Nature Communications*, 9(1):3312. https://doi.org/10.1038/s41467-018-05862-6
Napolitano, G., Malta, C.D., Ballabio, A., 2022. Non-canonical mTORC1 signaling at the lysosome. *Trends in Cell Biology*, 32(11):920–931. https://doi.org/10.1016/j.tcb.2022.04.012
Nixon, R.A., 2013. The role of autophagy in neurodegenerative disease. *Nature Medicine*, 19(8):983–997. https://doi.org/10.1038/nm.3232
Nixon, R.A., Rubinsztein, D.C., 2024. Mechanisms of autophagy-lysosome dysfunction in neurodegenerative diseases. *Nature Reviews. Molecular Cell Biology*, 25(11):926–946. https://doi.org/10.1038/s41580-024-00757-5
Nogueira-Machado, J.A., Rocha-Silva, F., Gomes, N.A., 2025. The Role of mTOR in Amyotrophic Lateral Sclerosis. *Biomedicines*, 13(4):952. https://doi.org/10.3390/biomedicines13040952
Okumura, F., Joo-Okumura, A., Nakatsukasa, K., *et al.*, 2016. The role of cullin 5-containing ubiquitin ligases. *Cell Division*, 11:1. https://doi.org/10.1186/s13008-016-0016-3
Olney, N.T., Alquezar, C., Ramos, E.M., *et al.*, 2017. Linking tuberous sclerosis complex, excessive mTOR signaling, and age-related neurodegeneration: a new association between TSC1 mutation and frontotemporal dementia. *Acta neuropathologica*, 134(5):813–816. https://doi.org/10.1007/s00401-017-1764-0
Ondaro, J., Hernandez-Eguiazu, H., Garciandia-Arcelus, M., *et al.*, 2022. Defects of Nutrient Signaling and Autophagy in Neurodegeneration. *Frontiers in Cell and Developmental Biology*, 10. https://doi.org/10.3389/fcell.2022.836196
Palmieri, M., Impey, S., Kang, H., *et al.*, 2011. Characterization of the CLEAR network reveals an integrated control of cellular clearance pathways. *Human Molecular Genetics*, 20(19):3852–3866. https://doi.org/10.1093/hmg/ddr306
Panwar, V., Singh, A., Bhatt, M., *et al.*, 2023. Multifaceted role of mTOR (mammalian target of rapamycin) signaling pathway in human health and disease. *Signal Transduction and Targeted Therapy*, 8:375. https://doi.org/10.1038/s41392-023-01608-z
Papadopoulos, C., Meyer, H., 2017. Detection and Clearance of Damaged Lysosomes by the Endo-Lysosomal Damage Response and Lysophagy. *Current biology: CB*, 27(24):R1330–R1341. https://doi.org/10.1016/j.cub.2017.11.012
Paul, S., Dansithong, W., Figueroa, K.P., *et al.*, 2021. Staufen1 in Human Neurodegeneration. *Annals of Neurology*, 89(6):1114–1128. https://doi.org/10.1002/ana.26069
Picot, M., Hifdi, N., Vaucourt, M., *et al.*, 2026. Lysosomal phosphoinositide turnover acts upstream of RagGTPase-mTORC1 and controls muscle growth. *Nature Metabolism*, . https://doi.org/10.1038/s42255-026-01484-1
Querfurth, H., Lee, H.-K., 2021. Mammalian/mechanistic target of rapamycin (mTOR) complexes in neurodegeneration. *Molecular Neurodegeneration*, 16(1):44. https://doi.org/10.1186/s13024-021-00428-5
Radulovic, M., Schink, K.O., Wenzel, E.M., *et al.*, 2018. ESCRT-mediated lysosome repair precedes lysophagy and promotes cell survival. *The EMBO journal*, 37(21):e99753. https://doi.org/10.15252/embj.201899753
Roczniak-Ferguson, A., Petit, C.S., Froehlich, F., *et al.*, 2012. The Transcription Factor TFEB Links mTORC1 Signaling to Transcriptional Control of Lysosome Homeostasis. *Science signaling*, 5(228):ra42. https://doi.org/10.1126/scisignal.2002790
Sancak, Y., Peterson, T.R., Shaul, Y.D., *et al.*, 2008. The Rag GTPases Bind Raptor and Mediate Amino Acid Signaling to mTORC1. *Science*, 320(5882):1496–1501. https://doi.org/10.1126/science.1157535
Sardiello, M., Ballabio, A., 2009. Lysosomal enhancement: a CLEAR answer to cellular degradative needs. *Cell Cycle (Georgetown, Tex.)*, 8(24):4021–4022. https://doi.org/10.4161/cc.8.24.10263
Sardiello, M., Palmieri, M., di Ronza, A., *et al.*, 2009. A gene network regulating lysosomal biogenesis and function. *Science (New York, N.Y.)*, 325(5939):473–477. https://doi.org/10.1126/science.1174447

Savini, M., Zhao, Q., Wang, M.C., 2019. Lysosomes: Signaling Hubs for Metabolic Sensing and Longevity. *Trends in Cell Biology*, 29(11):876–887. https://doi.org/10.1016/j.tcb.2019.08.008

Saxena, S., Roselli, F., Singh, K., *et al.*, 2013. Neuroprotection through excitability and mTOR required in ALS motoneurons to delay disease and extend survival. *Neuron*, 80(1):80–96. https://doi.org/10.1016/j.neuron.2013.07.027

Saxton, R.A., Sabatini, D.M., 2017. mTOR Signaling in Growth, Metabolism, and Disease. *Cell*, 168(6):960–976. https://doi.org/10.1016/j.cell.2017.02.004

ScottOri, SaranEkambir, A, F., 2025. The spectrum of lysosomal stress and damage responses: from mechanosensing to inflammation. *EMBO Reports*, . https://doi.org/10.1038/s44319-025-00405-9

Shao, Q., Yang, M., Liang, C., *et al.*, 2020. C9orf72 and smcr8 mutant mice reveal MTORC1 activation due to impaired lysosomal degradation and exocytosis. *Autophagy*, 16(9):1635–1650. https://doi.org/10.1080/15548627.2019.1703353

Shariq, M., Khan, M.F., Raj, R., *et al.*, 2024. PRKAA2, MTOR, and TFEB in the regulation of lysosomal damage response and autophagy. *Journal of Molecular Medicine*, 102(3):287–311. https://doi.org/10.1007/s00109-023-02411-7

Shaw, R.J., Bardeesy, N., Manning, B.D., *et al.*, 2004. The LKB1 tumor suppressor negatively regulates mTOR signaling. *Cancer Cell*, 6(1):91–99. https://doi.org/10.1016/j.ccr.2004.06.007

Skowyra, M.L., Schlesinger, P.H., Naismith, T.V., *et al.*, 2018. Triggered recruitment of ESCRT machinery promotes endolysosomal repair. *Science*, 360(6384):eaar5078. https://doi.org/10.1126/science.aar5078

Stavrides, P., Goulbourne, C.N., Peddy, J., *et al.*, 2025. mTOR inhibition in Q175 Huntington's disease model mice facilitates neuronal autophagy and mutant huntingtin clearance. *bioRxiv*, :2024.05.29.596471. https://doi.org/10.1101/2024.05.29.596471

Takahara, T., Amemiya, Y., Sugiyama, R., *et al.*, 2020. Amino acid-dependent control of mTORC1 signaling: a variety of regulatory modes. *Journal of Biomedical Science*, 27(1):87. https://doi.org/10.1186/s12929-020-00679-2

Talaia, G., Bentley-DeSousa, A., Ferguson, S.M., 2024. Lysosomal TBK1 responds to amino acid availability to relieve Rab7-dependent mTORC1 inhibition. *The EMBO Journal*, 43(18):3948–3967. https://doi.org/10.1038/s44318-024-00180-8

Tan, J.X., Finkel, T., 2022. A phosphoinositide signalling pathway mediates rapid lysosomal repair. *Nature*, 609(7928):815–821. https://doi.org/10.1038/s41586-022-05164-4

Tan, J.X., Finkel, T., 2023. Lysosomes in senescence and aging. *EMBO Reports*, 24(11):e57265. https://doi.org/10.15252/embr.202357265

Thurston, T.L.M., Wandel, M.P., von Muhlinen, N., *et al.*, 2012. Galectin 8 targets damaged vesicles for autophagy to defend cells against bacterial invasion. *Nature*, 482(7385):414–418. https://doi.org/10.1038/nature10744

Udayar, V., Chen, Y., Sidransky, E., *et al.*, 2022. Lysosomal dysfunction in neurodegeneration: emerging concepts and methods. *Trends in neurosciences*, 45(3):184–199. https://doi.org/10.1016/j.tins.2021.12.004

Valenstein, M.L., Wranik, M., Lalgudi, P.V., *et al.*, 2025. Structural basis for the dynamic regulation of mTORC1 by amino acids. *Nature*, 646(8084):493–500. https://doi.org/10.1038/s41586-025-09428-7

Walker, S.A., Ktistakis, N.T., 2020. Autophagosome Biogenesis Machinery. *Journal of Molecular Biology*, 432(8):2449–2461. https://doi.org/10.1016/j.jmb.2019.10.027

Wang, F., Gómez-Sintes, R., Boya, P., 2018. Lysosomal membrane permeabilization and cell death. *Traffic (Copenhagen, Denmark)*, 19(12):918–931. https://doi.org/10.1111/tra.12613

Wu, Y., Li, T., Jiang, X., *et al.*, 2025a. (−)-Epicatechin Rescues Memory Deficits by Activation of Autophagy in a Mouse Model of Tauopathies. *MedComm*, 6(4):e70144. https://doi.org/10.1002/mco2.70144

Wu, Y., Liu, X., Luo, G., *et al.*, 2025b. DNLA Delayed the Appearance of Learning and Memory Impairment of APP/PS1 Mice: Involvement of mTOR/TFEB/v-ATPase Signaling Pathway. *CNS Neuroscience & Therapeutics*, 31(3):e70300. https://doi.org/10.1111/cns.70300

Yang, S., Zhang, Y., Ting, C.-Y., *et al.*, 2020. The Rag GTPase Regulates the Dynamic Behavior of TSC Downstream of Both Amino Acid and Growth Factor Restriction. *Developmental Cell*, 55(3):272-288.e5. https://doi.org/10.1016/j.devcel.2020.08.006

Yip, C.K., Murata, K., Walz, T., *et al.*, 2010. Structure of the Human mTOR Complex I and Its Implications for Rapamycin Inhibition. *Molecular Cell*, 38(5):768–774. https://doi.org/10.1016/j.molcel.2010.05.017

Zajac, M., Mukherjee, S., Anees, P., *et al.*, 2024. A mechanism of lysosomal calcium entry. *Science Advances*, 10(7):eadk2317. https://doi.org/10.1126/sciadv.adk2317

Zhang, X., Li, L., Chen, S., *et al.*, 2011. Rapamycin treatment augments motor neuron degeneration in SOD1(G93A) mouse model of amyotrophic lateral sclerosis. *Autophagy*, 7(4):412–425. https://doi.org/10.4161/auto.7.4.14541

Zhao, R., Huang, S., Li, J., *et al.*, 2024. Excessive STAU1 condensate drives mTOR translation and autophagy dysfunction in neurodegeneration. *The Journal of Cell Biology*, 223(8):e202311127. https://doi.org/10.1083/jcb.202311127

Zhu, S., Yao, R., Li, Y., *et al.*, 2020. Lysosomal quality control of cell fate: a novel therapeutic target for human diseases. *Cell Death & Disease*, 11(9):817. https://doi.org/10.1038/s41419-020-03032-5