



REVIEW ARTICLE

ER-phagy receptors: structural mechanisms in selective ER degradation and disease implications

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The endoplasmic reticulum (ER) is a central organelle for protein synthesis and folding, lipid metabolism and calcium signaling, etc. To maintain ER homeostasis, cells employ a specific autophagy process termed ER-phagy (reticulophagy), which degrades ER components via three forms: macro-ER-phagy (involving bulk ER sequestration), micro-ER-phagy (lysosome-direct), and ER-to-lysosome-associated degradation (ERLAD). The identification of specific ER-phagy receptors including FAM134A, FAM134B, FAM134C, TEX264, SEC62, RTN3L, CCPG1, ATL3, CALCOCO1 and others has significantly advanced our understanding of ER quality control mechanisms. In this review we summarize the current knowledge on ER-phagy receptors, and emerging evidence linking ER-phagy dysfunction to various disease pathologies including neurological disorders, cancer, metabolic diseases, cardiovascular diseases, infections and immune disorders. Recent evidence shows that ER-phagy receptors can form novel ER-derived structures, such as ER-tubular bodies (ER-TBs) consisted of ATL3 and RTN3L, which mediate Golgi-bypassing unconventional protein secretion under stress conditions, revealing non-degradative functions of these receptors beyond quality control. Targeting ER-phagy receptors may provide insights into potential therapeutic strategies for diseases associated with this fundamental cellular process.

Keywords: endoplasmic reticulum; ER-phagy; ER-phagy receptors; FAM134B; TEX264; human diseases

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INTRODUCTION

The endoplasmic reticulum (ER), characterized by its unique structure and specialized functions, plays a pivotal role in numerous cellular processes. These processes include protein folding and post-translational modification, protein quality control, lipid and hormone synthesis, calcium homeostasis, metabolic regulation and intercellular communication [1, 2]. Interconnected and widely distributed throughout the cytoplasm, the ER forms a dynamic network capable of altering its structure, composition, and morphology in response to metabolites, developmental signals, or proteotoxic stress to maintain its functional integrity. Autophagy is a conserved eukaryotic degradation mechanism, from yeast to humans, that enables the removal and recycling of misfolded proteins and damaged organelles. Typically activated by stress or nutrient deprivation, autophagy serves functions that extend beyond degradation and recycling proteins, facilitating the clearance of damaged or dysfunctional organelles. Autophagy can occur in either a non-selective or selective manner. Selective autophagy comprises distinct pathways that target specific substrates for degradation, such as mitophagy, lysophagy, ribophagy, lipophagy, nucleophagy, ER-phagy and so on, depending on the substrate, and substrate recognition is determined by selective autophagy receptors [3]. Endoplasmic reticulum autophagy (ER-phagy), also known as reticulophagy, is a selective degradation process that occurs both under normal physiological states and in response to cellular stressors such as nutrient deprivation, unfolded protein response (UPR) activation, toxin

exposure, and other internal or external environmental challenges. ER-containing autophagosomes were first observed by Bernales et al. in 2007 using electron microscopy. They demonstrated that ER stress induces selective ER-targeted autophagy in yeast, primarily functioning to degrade excess ER membranes and regulate ER volume to maintain cellular homeostasis [4].

Given the diverse functional and structural domains of the ER and its responsiveness to various intra- and extracellular stimuli or stresses, the proper execution of ER-phagy requires multiple regulatory mechanisms to maintain homeostasis. In recent years, significant advances in ER-phagy research have led to the identification of several novel ER-phagy receptors and revealed critical connections between ER-phagy and various human diseases, including neurodegenerative diseases, cancer, metabolic disorders, inflammation, infection and cardiovascular diseases (CVDs). This review summarizes recent advances in ER-phagy mechanisms and receptors, emphasizing their roles in various diseases to further elucidate ER-phagy's contribution to cellular homeostasis and disease pathogenesis.

THE PROCESS OF ER-PHAGY

In cells, most secreted and membrane proteins are synthesized, folded, and assembled within the ER. Proper protein folding and processing are ensured by abundant ER-resident chaperones and the maintenance of a stable ER microenvironment [5]. When cells encounter external or internal stressors that disrupt protein

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folding, unfolded or misfolded proteins accumulate in the ER, leading to a disturbance of ER homeostasis—known as endoplasmic reticulum stress (ER stress). To re-establish homeostasis, cells activate the UPR, which enhances the folding capacity of the ER, attenuates overall protein synthesis and promotes ER-associated protein degradation (ERAD). In ERAD, misfolded proteins are eliminated through both the ubiquitin–proteasome system and autophagy-related pathways [6]. However, the substrate of ERAD is limited to proteins, whereas autophagy can remove portions of the ER [7]. The maintenance of ER quality control relies on the coordinated action of both systems.

It has been shown that prolonged or excessive ER stress and sustained UPR not only trigger non-selective macro-autophagy but also induce ER-phagy. During ER-phagy, autophagosomes specifically engulf ER fragments without incorporating other organelles or cytoplasmic contents [8, 9]. Depending on its reliance on macro-autophagy machinery, ER-phagy can be classified into macro-ER-phagy and micro-ER-phagy.

Macro-ER-phagy

Macro-ER-phagy is the most representative and prevalent of the three types of ER-phagy. It proceeds through multiple coordinated steps involving specific ER-resident receptors and the core autophagic machinery to mediate the degradation of ER components. During macro-ER-phagy, portions of the ER are sequestered together with cytoplasmic materials into double-membraned autophagosomes, which fuse with lysosomes to degrade their contents. This process is normally mediated by ER-associated receptors and targets the ER for autophagosome delivery [10, 11]. In response to various stressors—such as UPR, protein aggregation, nutrient deficiency, or disruptions in ER structure—specific ER-phagy receptors identify and label ER components destined for degradation. Concurrently, cells activate the autophagosome initiation complex by either inhibiting mTOR or activating AMPK to directly phosphorylate Atg1/ULK1 (serine/threonine protein kinase ULK1, a mammalian homologue of Atg1). This event initiates the formation of the isolation membrane. The ubiquitin-like proteins such as Atg8/LC3/GABARAP are recruited to the expanding membrane, promoting its elongation and enabling

the binding of ER-phagy receptors. Subsequently, as the isolation membrane encloses the targeted ER fragments, mature autophagosomes are formed, which later fuse with lysosomes to degrade the engulfed ER components and associated receptors [2, 12, 13].

Micro-ER-phagy

In micro-ER-phagy, portions of the ER are directly engulfed by invaginations of the vacuolar or lysosomal membrane and delivered into the lysosomal lumen for degradation. This process occurs independently of autophagosome formation and generally does not require specific receptor mediation. In yeast, when ER stress or over-expansion occurs, a portion of the ER can form ER whorls, which are internalized by the invaginated vesicular membrane into the vesicle and subsequently degraded [14]. In mammalian cells, mutant type I procollagen proteins can be recruited to ER exit sites (ERES), where they colocalize with COP II coat proteins and autophagy-associated proteins (SQSTM1, LC3, etc.). These protein-enriched ERES regions are subsequently ubiquitinated and delivered to lysosomes for degradation through a mechanism resembling micro-autophagy [15]. Recent studies have further elucidated that micro-ER-phagy can be a highly selective process. Under nutrient stress, aberrant membrane proteins are cleared via a TORC1-dependent micro-ER-phagy pathway requiring the ubiquitin ligase Rsp5, its adaptor Ssh4, and the ESCRT complex [16].

ER-to-lysosome-associated degradation (ERLAD)

In addition to macro- and micro-ER-phagy, lysosomes can also fuse directly with ER-derived vesicles to mediate their degradation. This process depends on ER-phagy receptor mediation but does not involve autophagosome formation, a process termed ER-to-lysosome-associated degradation (ERLAD, Fig. 1) [17].

Secretory ER-phagy pathway

Beyond degradative pathways, a novel secretory ER-phagy route has been identified. The assembly of RAB22A, TMEM33, and RTN4 drives the formation of ER-derived non-canonical autophagosomes that bypass lysosomal degradation. Instead, these vesicles are secreted as RAB22A-induced extracellular vesicles (R-EVs) via a

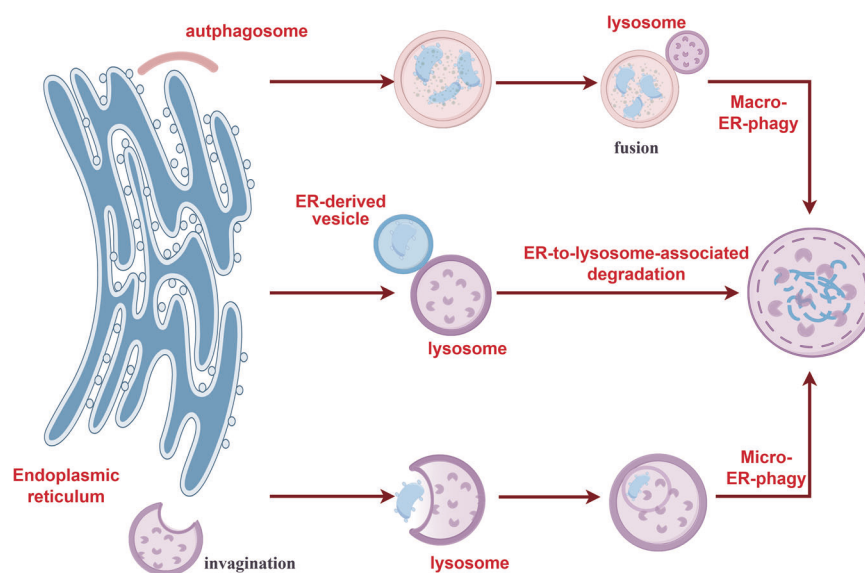


Fig. 1 Different types of ER-phagy. In macro-ER-phagy, ER fragments are sequestered by double-membraned autophagosomes along with other cytoplasmic components. The autophagosomes, which are formed from isolation membranes, subsequently fuse with lysosomes, leading to the degradation of their contents. In micro-ER-phagy, the vacuolar or lysosomal membrane invaginates, allowing portions of the ER to be internalized directly into the lysosomal lumen for degradation. In ERLAD, the lysosome fuses directly with ER-derived vesicles, leading to the degradation of the vesicular contents.

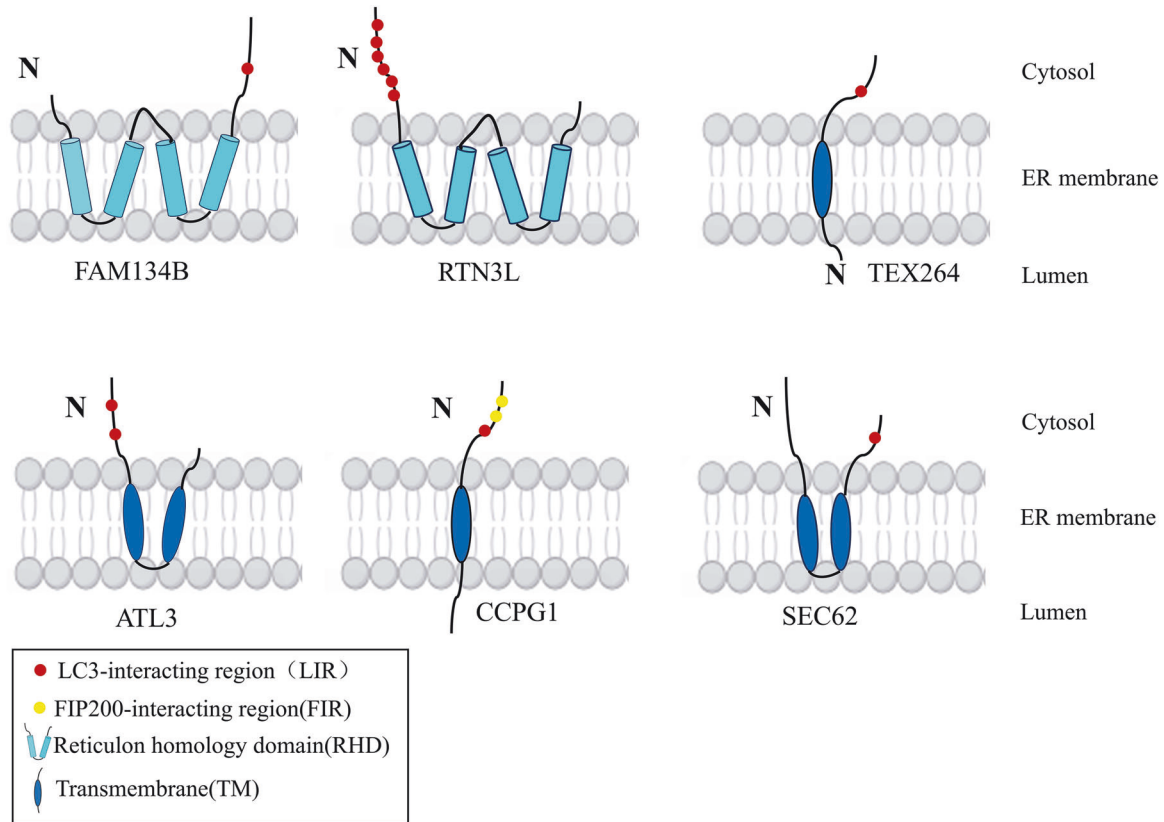


Fig. 2 Structural characterization of ER-phagy receptors. FAM134B and RTN3L contain RHD structural domains. All receptors contain at least one LIR in their cytoplasmic regions. CCPG1 also contains two FIR motifs.

newly discovered MVB-like organelle termed the Rafeosome, establishing a direct link between ER-phagy and extracellular vesicle secretion [18].

ER-PHAGY RECEPTORS

ER-phagy receptors serve as key regulators of ER-phagy activity, and their discovery has significantly advanced the understanding of the diverse mechanisms underlying this process. To date, two resident ER membrane receptors have been identified in yeast, Atg39 and Atg40. In yeast, the Lst1-Sec23 complex binds to the stress-induced autophagy receptor Atg40 to mediate ER-phagy, thereby preventing protein accumulation in the ER and maintaining cellular homeostasis [19]. In mammalian cells, a growing number of ER-phagy receptors have been characterized, including family with sequence similarity 134 (FAM134) proteins (FAM134A, FAM134B, FAM134C), reticulon-3L (RTN3L), cell cycle progression protein 1 (CCPG1), translocation protein 1 (SEC62), testis-expressed protein 264 (TEX264), atlastin-3 (ATL3), calcium binding and coiled-coil domain 1 (CALCOCO1), sequestosome 1 (SQSTM1/p62) and CDK5 regulatory subunit associated protein 3 (CDK5RAP3). Generally, ER-phagy receptors are classified into two major structural classes. The first group comprises receptors that contain a reticulon homology domain (RHD) (such as mammalian FAM134 proteins and RTN3L, as well as yeast Atg40)—where the RHD anchors the receptor to the ER membrane and promotes membrane curvature and remodeling. The second group lacks an RHD, including mammalian SEC62, TEX264, and C53, as well as yeast Atg39 [20]. Among these, some ER-phagy receptors are ER-resident membrane proteins such as FAM134B, SEC62, RTN3L, CCPG1, ATL3, TEX264, while others, such as CALCOCO1, are cytosolic and function in specific ER regions [20]. In mammals, ER-phagy receptors execute their function by

binding to ubiquitin-like Atg8 family (LC3 and GABARAP) through the LC3-interacting region (LIR) motif, thereby linking ER membrane or tubule domains to autophagosomes [9, 12, 21]. Certain ER-phagy receptors interact and cooperate with FIP200 (the yeast homolog Atg11), a component of the ULK complex responsible for initiating autophagy [22–25] (Fig. 2, and Table 1).

FAM134

The FAM134 family of reticulon proteins serves as a key receptor group in ER-phagy and is believed to participate in the early initiation of this process [26]. The family includes three conserved ER-resident proteins: FAM134A, FAM134B and FAM134C [27].

FAM134B, an ER-resident protein, was the first ER-phagy receptor identified in mammals and remains the most extensively studied to date. It acts primarily at the curved edges of the ER sheets, targeting the sheet ER for degradation. Loss of FAM134B impairs the autophagic clearance of the ER, resulting in abnormal ER expansion and heightened cellular sensitivity to stressors such as ER stress and nutrient deprivation. Conversely, overexpression of FAM134B induces ER fragmentation and lysosomal degradation [28]. Structurally, the N-terminus of the FAM134B contains a RHD structure. Aggregation of RHD structures increases the curvature of the lipid bilayer, facilitating vesicle formation during ER-phagy [29]. The C-terminus has an intrinsically disordered region (IDR) that detects membrane curvature. Through interaction with the RHD, the IDR promotes membrane remodeling and facilitates protein clustering, thereby accelerating vesicle budding and enhancing RHD-mediated membrane dynamics [30]. The IDR also contains LIR motifs capable of binding GABARAP/LC3, bridging ER cargo with autophagosomes and regulating both macro-ER-phagy and LC3-dependent vesicular trafficking [20]. The interaction between FAM134B and LC3 provides additional force for ER budding, leading to ER membrane fission and subsequent

Table 1. Properties and pathways of key ER-phagy receptors.

	FAM134B	RTN3L	TEX264	ATL3	CCPG1	SEC62
Size	497aa	1032aa	313aa	541aa	757aa	399aa
IDR	Yes	Yes	Yes	No	Yes	Yes
Localization	Sheet	Tubule	3-way junctions	Tubule	Sheet tubule	Sheet tubule
Type of ER-phagy	Macro-ER-phagy ERLAD	Macro-ER-phagy	Macro-ER-phagy	Macro-ER-phagy	Macro-ER-phagy	Macro-ER-phagy Micro-ER-phagy

FAM134B family with sequence similarity 134 member B, *RTN3L* reticulon-3L, *TEX264* testis-expressed protein 264, *ATL3* atlastin-3, *CCPG1* cell cycle progression protein, *SEC62* translocation protein SEC62.

lysosomal degradation [31]. Recent studies highlight the IDR as a core functional module among ER-phagy receptors. These IDRs share conserved features, including a net negative charge, a length exceeding 47 amino acids, and a minimum distance of 24 residues between the LIR motif and the membrane. Notably, these IDRs are functionally interchangeable across organelles: when transplanted to the mitochondrial outer membrane, the IDR of an ER-phagy receptor induces mitochondrial fragmentation and mitophagy. Conversely, transplanting the IDR of the mitophagy receptor FUNDC1 to the ER membrane can trigger ER-phagy [32]. Thus, both the RHD and the IDR containing the LIR motif constitute the two essential structural domains of FAM134B-mediated ER-phagy.

Phosphorylation of the RHD, together with phosphorylation-dependent ubiquitination of FAM134B, is essential for receptor aggregation at the ER membrane and for initiating ER-phagy [33]. The E3 ubiquitin-ligase autocrine motility factor receptor (AMFR) catalyzes FAM134B ubiquitination, promoting FAM134B aggregation and enhancing ER-phagy [34]. Interestingly, another RHD-containing ER-shaping protein, ADP ribosylation factor like GTPase 6 interacting protein 1 (ARL6IP1), interacts with FAM134B to form heteromeric multi-protein clusters essential for ER-phagy, and its ubiquitination further facilitates this process [35]. However, VAMP-associated proteins (VAPs) recruit ubiquitin specific peptidase 20 (USP20) to the ER, where USP20 specifically removes ubiquitin from FAM134B, stabilizing the receptor and promoting its interaction with LC3B to enhance ER-phagy [36].

Further studies showed that FAM134B acts synergistically with autophagy-related protein 5 (Atg5), Beclin-1 and FIP200 in the ER-phagy process [37]. FAM134B-mediated ER-phagy is also regulated by CREB-binding protein (CBP) and SIRT7. Under ER stress conditions, CBP acetylates FAM134B at lysine 160, triggering calcium-calmodulin (CaM)-dependent protein kinase II (CAMK II)-mediated phosphorylation at serine 151 and activating ER-phagy. Conversely, SIRT7 deacetylates FAM134B, suppressing ER-phagy [38]. Interestingly, FAM134B also promotes mitophagy by interacting with optic atrophy 1 (OPA1) [39], suggesting that FAM134B not only serves as a key receptor in ER-phagy but also participates in other selective autophagy pathways. In addition, its transcription is regulated by the transcription factors TFEB and TFE3, whose nuclear translocation upregulates FAM134B expression, promoting the delivery of ER fragments to lysosome [40, 41]. Interestingly, Sestrin2 (SESN2) is a highly conserved stress-responsive protein induced by ER storage disorders, and SESN2 also enhances ER-phagy by inhibiting mTORC1-dependent phosphorylation of TFEB/TFE3, thereby enabling their nuclear translocation and subsequent activation of FAM134B and lysosomal genes. Recent work has revealed isoform-specific transcriptional reprogramming of FAM134B during cell differentiation. During myogenesis, the canonical FAM134B1 isoform is degraded, while FAM134B2 is upregulated, driving extensive ER remodeling through precisely regulated ER-phagy to support muscle differentiation [42].

Both FAM134A and FAM134C can induce membrane outgrowth, but at a slower rate than FAM134B. They promote

ER division in a LIR-dependent manner but through distinct mechanisms [27]. Specifically, FAM134C is phosphorylated by casein kinase 2 (CK2). During starvation, inhibition of mTORC1 reduces FAM134C phosphorylation, enhances its interaction with LC3, and promotes FAM134C-mediated ER-phagy activation [43].

RTN3L

RTN3, a member of the reticulon family, is predominantly localized to the tubular ER. It contains a C-terminal RHD domain that anchors the protein to the ER membrane and facilitates membrane curvature. RTN3 exists in multiple splicing variants, among which only the long isoform, RTN3L, harbors six functional LIR motifs. These motifs are essential for binding LC3/GABARAP, fragmenting ER tubules, and mediating its function as an ER-phagy receptor. During nutrient deprivation, RTN3L oligomerizes, leading to the segmentation of ER tubules into discrete fragments and recruitment of LC3B, thereby promoting lysosomal delivery and degradation of ER-derived tubule fragments [44]. Beyond its interaction with LC3/GABARAP, the LIR motifs of RTN3L also perform additional regulatory roles. Under nutrient-replete conditions, RTN3L associates with the FSV structural domain of Rab9a via its LIRs and aggregates at membrane contact sites between the ER and late endosomes, thereby regulating endosomal formation and substrate recognition [45].

Interestingly, RTN3L mediates ER-phagy independently of FAM134B. In FAM134B-deficient mouse embryonic fibroblasts, loss of RTN3L impairs starvation-induced turnover of ER tubules without affecting global autophagic flux or overall ER morphology. Conversely, FAM134B deletion does not interfere with RTN3L-mediated ER tubule fragmentation. Immunoprecipitation analysis showed that FAM134B preferentially interacts with RTN2L rather than RTN3L and shows stronger affinity for proteins involved in autophagic vesicle formation, such as VTI1B (vesicle transport through interaction with t-SNAREs 1B), syntaxin 8 (STX8) and Ca²⁺-related ER proteins. Collectively, these data suggest that RTN3L and FAM134B act as distinct and independent ER-phagy receptors that cooperate to preserve ER homeostasis [44, 46].

PTEN induced putative kinase 1 (PINK1) facilitates the recruitment of the E3 ubiquitin ligase Parkin to damaged mitochondria, activating Parkin-mediated ubiquitination of mitochondrial surface substrates, which in turn drives mitophagy through proteasomal or lysosomal degradation pathways [47]. Notably, emerging evidence indicates that both PINK1 and Parkin also contribute to ER clearance by modulating ER-phagy receptor abundance. Specifically, PINK1 deficiency decreases RTN1L levels and ER-phagy flux, whereas Parkin exerts an opposite effect by upregulating RTN1L levels and enhancing ER-phagy activity [48].

TEX264

TEX264 has been independently identified as a novel ER-phagy receptor [49–51]. It is an ER transmembrane protein localized to both ER lamellae and tubules, and can be delivered to lysosomes. Fluorescence observations showed that under nutrient-rich

conditions, TEX264 displays a reticular distribution, whereas under starvation it forms punctate structures, thereby promoting starvation-induced ER-phagy [50]. The N-terminus of TEX264 resides in the ER lumen, while the C-terminus in the cytoplasm. The cytoplasmic region contains a canonical LIR motif and a long IDR. The presence of IDRs is a common feature among ER-phagy receptors, enabling them to bridge the ER and the growing autophagosomal membrane. In mammalian cells, TEX264 interacts with Atg8 family proteins via LIR motif, showing a preferential binding affinity for LC3A, LC3B, and GABARAPL1 [12]. Thus, both the LIR and IDR are indispensable for the receptor's autophagic function [50]. The core LIR motif of TEX264 contains a serine residue that can be phosphorylated by CK2. This phosphorylation is required for its interaction with Atg8, autophagosomal localization, and receptor activation, while multiple phosphorylation events further enhance its binding affinity for Atg8 [52]. During ER-phagy, TEX264 binds to LC3 at the three-way junction of the ER tubule, suggesting that these junctions may serve as sites where ER segments are enclosed by autophagosomes. Additionally, TEX264 harbors a valosin-containing protein (VCP)-interacting SHP box motif at its C-terminus, which mediates direct association with VCP [53] (Fig. 3).

Studies have shown that activating transcription factor 4 (ATF4) serves as a potential regulator of TEX264-dependent ER-phagy, and is essential for ER stress-induced autophagic membrane elongation [54]. Loperamide (LOP) treatment has been shown to upregulate ATF4, which in turn induces the expression of ATF4-dependent autophagy genes (e.g. Atg13, WD Repeat Domain Phosphatidylinositide Interacting Protein 1(WIP1)), thereby enhancing TEX264-mediated ER-phagy. However, whether ATF4 specifically participates in ER stress-induced ER-phagy remains to be determined [55]. Furthermore, unlike FAM134C, CK2-mediated phosphorylation of TEX264 promotes ER-phagy by facilitating the binding of TEX264 to LC3/GABARAP family members [52].

Interestingly, TEX264 also exerts functions beyond its role as an ER-phagy receptor. It has been implicated in the regulation of DNA replication. During this process, eukaryotic topoisomerase 1 (TOP1) facilitates DNA replication and transcription; however, TOP1 forms a catalytic intermediate topoisomerase 1 cleavage

complex (TOP1cc) with DNA, leading to genomic instability and cell death. In human cells, p97 plays a crucial role in repairing TOP1cc lesions. Notably, TEX264 recruits p97 to TOP1cc through its SHP motif and binds TOP1 via its GyrI-like structural domain [51, 56]. Furthermore, TEX264 acts as a receptor for nucleophagy at DNA replication forks, mediating the degradation of TOP1cc via p97ATPase. This process depends on MRE11 and ATR kinase activity and facilitates lysosomal delivery of TOP1cc, thereby promoting DNA repair, enhancing cell survival, and maintaining genomic integrity [57].

ATLs

In mammals, three closely related ATLs (ATL1-3) regulate ER fusion, and their deficiency leads to altered ER morphology [21]. ATL proteins are believed to remodel the ER to facilitate fragmentation during autophagosome formation. Each ATL contains an N-terminal GTPase domain, a middle structural domain, two closely spaced hydrophobic fragments near the C-terminal end, and a cytoplasm C-terminal tail [58]. Sequence analyses reveal that ATL1, ATL2, and ATL3 share high structural and functional similarity, and these isoforms can partially compensate for each other during ER-phagy. ATL1 is involved in vesicle formation and the maintenance of ER structure and function in vivo [59], suggesting a potential role in ER-phagy. The localization of ATL2 to the ER is not only essential for maintaining ER morphology but also for regulating ER-phagy. ATL2 is proposed to act downstream of FAM134B to promote the removal of damaged ER [60]. ATL3 is enriched at tubular three-way junctions and binds specifically to GABARAPs via two N-terminus GABARAP-interacting motifs (GIMs). Its GTP domain enables trans-dimerization, which contributes to the degradation of the tubular ER. Mutations in either of the GIMs affect the binding of ATL3 to GABARAPs, whereas mutations in the GTP structural domain do not affect this interaction or its function in ER-phagy [58].

CCPG1

Among the different ER-phagy receptors, CCPG1 is of particular interest because it binds Atg8/LC3 protein and FIP200 through different motifs. These interactions with Atg proteins are crucial

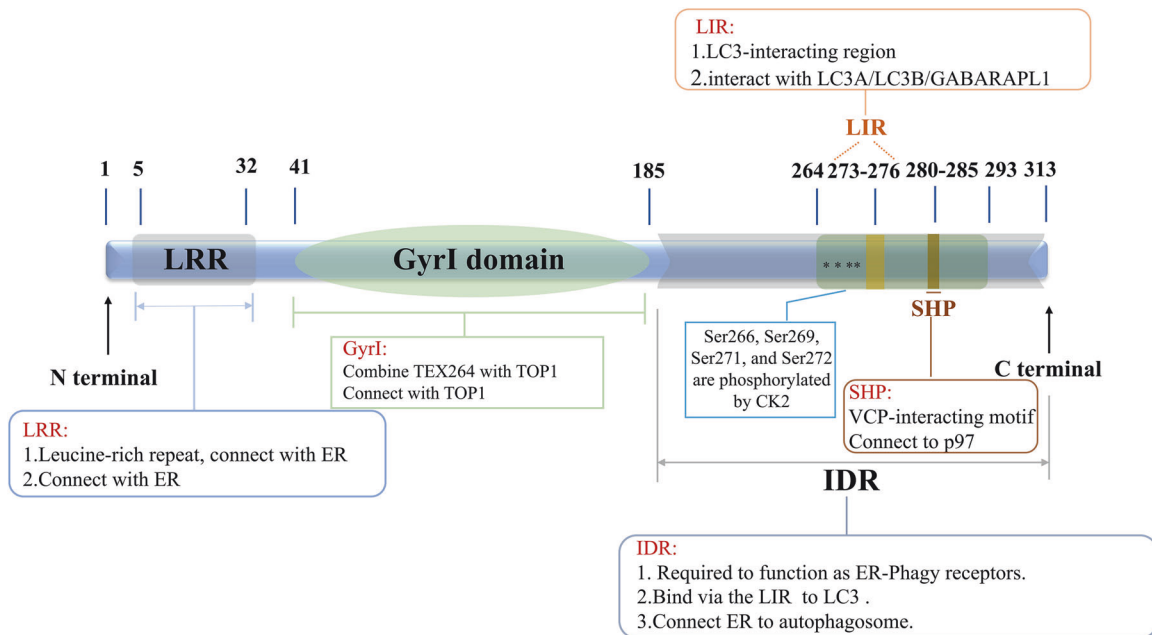


Fig. 3 Structural domain of TEX264. There is a leucine-rich repeat (LRR) at the N-terminus, an LC3-interacting region (LIR) motif and a VCP-interacting motif SHP box at the C-terminus, as well as a long intrinsically disordered region (IDR). In addition, there is a GyrI-like structural domain that binds TOP1.

for CCPG1-mediated ER-phagy [25]. Unlike most mammalian ER-phagy receptors, which typically bind only to GABARAP or LC3, CCPG1 is regarded as an atypical ER-phagy receptor. CCPG1 is a transmembrane protein that spans both the ER lumen and cytoplasm. Structurally, it comprises three distinct domains: an N-terminal cytoplasmic domain, a transmembrane segment embedded within the ER membrane, and a C-terminal domain [37]. Functionally, the luminal C-terminus protects against ER luminal protein aggregation and activation of the UPR, as well as against tissue damage in the exocrine pancreas [25]. The cytoplasmic N-terminus contains one LIR, which binds GABARAP/LC3, and two FIP200-interacting regions (FIRs), which associate with FIP200. It is thought that the LIR and FIRs recruit autophagosomal membranes, while the C-terminal structural domain recognizes and interacts with misfolded proteins [25]. Under starvation or ER stress, interaction of CCPG1 with LC3 proteins and FIP200 promotes the engulfment and clearance of CCPG1-containing ER fragments, thereby maintaining ER proteostasis [25].

SEC62

SEC62, also known as translocation protein 1, promotes the clearance of surplus ER that accumulates during cellular stress, including the UPR. This mechanism, referred to as recovER-phagy, is essential for restoring ER homeostasis [61]. SEC62 is an ER transmembrane protein localized to both lamellar and tubular regions, where it regulates the translocation of nascent polypeptides into the ER and participates in distinct forms of autophagy depending on cellular context. Specifically, SEC62 is involved in macro-ER-phagy during starvation [62] and micro-ER-phagy during recovery from stress [63]. The SEC62-mediated ER-phagy pathway is essential for alleviating ER stress. The C-terminal cytosolic domain of SEC62 contains a conserved LIR that mediates its interaction with LC3 proteins on the autophagosomal membrane, facilitating autophagosome–lysosome fusion and the degradation of ER fragments [37]; however, it is not required for its function in the protein translocation machinery [61]. The differential functional domains suggest that the LC3/GABARAP-binding site of SEC62 is distinct from its protein translocation interface [64, 65]. Consequently, SEC62 acts as a bifunctional protein, coordinating both protein import and stress recovery–associated ER turnover through distinct molecular mechanisms.

Other ER-phagy receptors

In addition to the above ER-phagy receptors, CALCOCO1 was identified as a soluble ER tubule-associated autophagy receptor that degrades ER tubules under conditions of proteotoxicity and starvation. Specifically, CALCOCO1 binds directly to Atg8 proteins through the LIR and UDS-interacting region domains and targets the ER by interacting with the VAP family of proteins through FFAT-like motifs [66]. However, unlike RTN3L and ATL3, which are also localized in ER tubules, CALCOCO1 does not participate in the formation of the ER-phagy site [67].

p62 (SQSTM1) has also been demonstrated to mediate ER-phagy and contribute to ER quality control. Specifically, p62 recognizes N-degron-modified ER proteins (such as BiP) through its ZZ domain and simultaneously binds to the K63-linked ubiquitin chains catalyzed by the ER-resident E3 ligase TRIM13. This interaction forms a p62–TRIM13–Nt-Arg complex, which subsequently drives ER-phagy [68].

C53 (CDK5RAP3/LZAP) is a conserved, non-canonical ER-phagy receptor found in plants and mammals. Unlike classical ER-membrane receptors, C53 is cytosolic and binds Atg8 via a shuffled Atg8-interacting motif. Under ER stress, it forms a complex with ubiquitin-fold modifier 1 (UFM1)-protein ligase 1 (UFL1) and DDRGK domain-containing protein 1 (DDRGK1) to sense ribosome stalling during signal recognition particle dependent translocation, thereby linking ribosome quality control

to ER-phagy [69, 70]. C53 mediates clearance of stalled complexes without affecting bulk autophagy and is essential for ER proteostasis [69].

Recent studies have identified the ER transmembrane protein ubiquitin-associated domain-containing protein 2 (UBAC2) as a novel ER-phagy receptor containing a conserved LIR motif. Under nutrient deprivation or ER-phagy activation, UBAC2 directly interacts with GABARAP and is degraded, while its expression does not alter overall autophagy flux. Functionally, UBAC2 suppresses the UPR in an ER-phagy-dependent manner, thereby contributing to the maintenance of ER homeostasis [71].

The cytoplasmic protein FK506-binding protein (FKBP) prolyl isomerase-like (FKBPL), which contains two LIR motifs that interact with LC3/GABARAP, can also mediate ER-phagy. Unlike other autophagy receptors, FKBPL specifically requires CKAP4 as a bridging molecule to connect with the ER. ER stress enhances the interaction between FKBPL and CKAP, leading to FKBPL oligomerization on the ER and subsequently inducing ER-phagy [72].

MEASUREMENT OF ER-PHAGY FLUX

Accurate monitoring of ER-phagy is crucial for elucidating its molecular mechanisms, pathophysiological functions, and potential therapeutic targets. Current primary methods for detecting and quantifying ER-phagy include electron microscopy for ultrastructural characterization, Western blot for biochemical assessment, and fluorescence imaging for spatiotemporal visualization. These techniques have their own advantages and limitations and often need to be combined for mutual verification.

Electron microscopy (EM)

Electron microscopy, with its nanometer-range resolution [73], allows direct visualization of ultrastructural alterations in cellular membranes and remains widely considered the gold standard for defining autophagic processes [74], including ER-phagy. This technique can capture moments when the endoplasmic reticulum lumen and characteristic structures (such as rough ER decorated with ribosomes) are sequestered by autophagosomes, thereby providing direct morphological evidence for ER-phagy. However, EM is technically demanding, time-consuming, and unsuitable for quantitative analysis, making it primarily a confirmatory method rather than a routine one.

Western blot

Western blot is the most fundamental and widely used biochemical method for detecting ER-phagy. Detection largely depends on the selection of specific ER markers. Currently, the most widely used indicator for monitoring autophagy flux is the analysis of LC3B protein levels by Western blot. It is generally accepted that the conversion of LC3B-I to LC3B-II observed [75] or increased LC3B-II level [76] indicates activation of autophagy flux. Furthermore, the degradation of selective autophagy substrates (such as SQSTM1/p62) and ER-phagy receptors (such as FAM134B, SEC62, RTN3L, CCPG1, ATL3) or ER luminal proteins (such as Calnexin, BiP/GRP78, PDI) can serve as indirect indicators of ER-phagy activity. This method allows for quantitative analysis of samples and is straightforward to perform, but it lacks spatial information, and its reliability depends heavily on the specificity and quality of the antibodies used.

Fluorescence microscopy and fluorescent biosensors

Fluorescence microscopy provides powerful spatiotemporal visualization of ER-phagy. Fusion proteins like GFP-LC3B can be used to detect LC3B via immunofluorescence or flow cytometry, observing LC3B puncta formation or total quantity changes. However, these methods cannot distinguish between LC3B-I and LC3B-II, only showing the total LC3B level. To address this limitation, several ER-targeted tandem fluorescent reporter constructs have been

developed. For example, by fusing an ER localization sequence with a RFP-GFP tandem fluorescent sequence, ER-phagy reporter vectors such as ssmRFP1-EGFP-KDEL [50] and mCherry-EGFP-RAMP4 [77], and ssRFP-GFP-KDEL [78] were constructed. Under basal conditions, red and green signals overlap, appearing yellow. When ER-phagy occurs, the acidic environment of the lysosome quenches the GFP, leaving only the red fluorescent signal.

Furthermore, fluorescent biosensors, as highly sensitive and specific tools for detecting intracellular activities with minimal invasiveness, have greatly advanced ER-phagy research [79]. Studies have shown that ER-phagy is accompanied by an increase in ER viscosity. A fluorescent probe containing a pentafluorophenyl ER-targeting group GE-Y was developed. By inhibiting intramolecular free rotation in high-viscosity environments, GE-Y significantly enhances the fluorescence signal, providing a novel tool for monitoring ER-phagy [80]. Similarly, YKI is a novel self-delivering ER-targeted viscosity sensor that has been applied to fluorescence lifetime imaging (FLIM). During autophagy, YKI translocates into lysosomes with ER fragments, where its fluorescence lifetime significantly increases, enabling accurate detection of ER-phagy without auxiliary lysosomal dyes [79].

Other innovative probes have expanded detection capabilities. ER-proRed, a novel dual-functional fluorescent probe, localizes to the ER under normal conditions and emits green fluorescence. During ER-phagy, it is co-delivered with ER fragments into acidic lysosomes, where the ROX-lactam unit is specifically activated, generating strong red fluorescence proportional to ER-phagy levels. Compared to commonly used fluorescent protein reporters, ER-proRed offers higher sensitivity, improved signal-to-noise ratio, and does not require plasmid transfection, making it widely applicable across cell models [81]. The signal-retaining autophagy indicator, composed of acid-insensitive blue fluorescent protein TOLLES (Tolerance of Lysosomal Environments) and acid-sensitive yellow fluorescent protein YPet, enables sensitive and quantitative analysis of ER-phagy flux via the TOLLES-to-YPet ratio. This system is compatible with high-content fixed-sample analysis and allows discrimination of ER-phagy pathways mediated by distinct receptors such as FAM134B and TEX264 [82]. Additionally, the ER-targeting fluorescent probe DHQM, based on the principles of aggregation-induced emission, specifically responds to peroxynitrite (ONOO⁻) as a marker of ER stress while simultaneously reporting ER-phagy activity. Its high resistance to quenching and strong emission make DHQM particularly valuable for investigating ER-phagy in complex disease models [83]. Collectively, these probes provide powerful and versatile platforms for dissecting the mechanisms and dynamics of ER-phagy.

In summary, ER-phagy detection relies on a combination of biochemical, imaging, and ultrastructural approaches. Western blot provides reliable quantitative assessment, fluorescence microscopy enables dynamic and spatial tracking, while electron microscopy delivers definitive structural validation. Looking ahead, methodological innovation is expected to further enhance ER-phagy research. The integration of gene-editing tools (such as CRISPR/Cas9-mediated tagging of endogenous ER-phagy receptors) with single-cell imaging techniques (for capturing cell-to-cell heterogeneity) [62, 84, 85] will provide a more comprehensive and mechanistic understanding of ER-phagy.

ER-PHAGY RECEPTORS AND DISEASE

Cells utilize ER-phagy to selectively eliminate damaged subregions of the ER and aberrantly accumulated luminal proteins, thereby preserving ER function and intracellular homeostasis. The identification of the first ER-phagy receptor, FAM134B, in mammals marked the beginning of molecular-level investigations into this process. Since then, growing evidence has revealed a strong connection between ER-phagy and various human diseases. As a fundamental cellular mechanism, ER-phagy is tightly regulated, and both its insufficient

and excessive activation have been implicated in the development of neurodegenerative disorders, cancer, metabolic syndromes, and infections. Consequently, the precise modulation of ER-phagy holds potential as a promising avenue for therapeutic intervention and disease prevention (Table 2).

Neurological diseases

During neurogenesis, specific ER-phagy receptors, such as the FAM134 family (FAM134A, FAM134B, FAM134C), TEX264 and CCPG1 proteins, regulate ER morphology and function by selectively removing ER proteins, thereby maintaining ER homeostasis and influencing protein secretion, neuronal development, and differentiation [26]. Specifically, calnexin delivers tropomyosin receptor kinase B (TrkB) to FAM134B for ER-phagy-mediated turnover to maintain normal development and function of the nervous system [86]. Conversely, loss-of-function mutations in FAM134B can lead to hereditary sensory and autonomic neuropathy type II (HSAN II), causing severe sensory deficits and autonomic dysfunction [87]. In contrast, the G216 mutant occurring in the FAM134B RHD structural domain exhibits hyperactive self-polymerisation and membrane cleavage, inducing aberrant ER breaks and excessive ER-phagy, which leads to sensory neuron death [88]. In addition, FAM134B and FAM134C control the axonal ER, and their combined deletion impairs motor and sensory functions in mice [28]. In the sciatic nerve of FAM134B/C knockout mice, expression of the ER-phagy receptor RTN3 was also markedly reduced compared to wild-type controls [89].

The ER is the primary site of protein folding and post-translational modification. ER-phagy eliminates misfolded proteins, preserves calcium homeostasis, and relieves ER stress, thereby playing a pivotal role in maintaining neuronal health. Dysregulation of ER-phagy has been implicated in several neurodegenerative diseases.

In Alzheimer's disease (AD), β -amyloid (A β) deposition is one of the pathogenic mechanisms of AD, and mutant amyloid precursor protein (APP) can accumulate in the ER and requires ER-phagy for degradation [90]. Recently, it has been reported that increasing the levels of ATL (corresponding to human ATL3) or RTNL1 (human RTN3) in the *Drosophila* brain moderately enhances ER-phagy and promotes the degradation of APP, thereby ameliorating APP toxicity and exerting a neuroprotective effect. Overexpression of these receptors in the *Drosophila* brain also significantly improves olfactory memory and prolongs lifespan in APP-overloaded flies [91]. Dysregulation of Ca²⁺ and N-linked glycosylation in AD leads to ER stress. Thapsigargin (Tg) is a non-competitive inhibitor of the ER Ca²⁺-ATPase, and tunicamycin (Tm) blocks protein N-glycosylation, leading to the UPR response and ER stress. In thapsigargin-resistant (TgR) and tunicamycin-resistant (TmR) hippocampal neuronal cells, sustained ER stress elevates RTN3L expression, enhancing ER-phagy and providing neuroprotection [92]. Interestingly, RTN3 interacts with beta-amyloid converting enzyme 1 (BACE1) to negatively regulate its activity, while elevated BACE1 levels are associated with increased APP processing [93]. In a mouse model of AD, RTN3 deficiency increases BACE1 levels and amyloid deposition. However, whether there is a link between RTN3L's function in ER-phagy and its role in regulating BACE1 activity remains to be investigated [46]. Moreover, A β -induced neuroinflammation, characterized by microglial activation and release of cytokines such as tumor necrosis factor- α (TNF- α) and interleukin (IL)-6, plays a key pathogenic role [94]. The furosemide analogue SI-W052 (4-chloro-N-furfuryl-5-(N-benzyl-N-methylsulfamoyl) anthranilic acid) potentiated TEX264-mediated ER-phagy, promotes ER turnover, suppresses ATF4 and spliced XBP1 expression, alleviates ER stress, and reduces IL-6 production, demonstrating an anti-inflammatory and neuroprotective effect. TEX264 is therefore a potential therapeutic target for neuroinflammation [95].

Table 2. Known diseases linked to ER-phagy receptors.

ER-phagy receptor	Related disease	Response	Reference
Neurodegenerative disease	FAM134B FAM134B FAM134B	FAM134B mutation causes sensory deficits and autonomic dysfunction Promote degradation of α -synuclein and recover of ER function Attenuate ER Ca^{2+} release and ROS production Reduce IP3R expression in MAMs, increase ER Ca^{2+} and decrease mitochondrial Ca^{2+}	[87] [98] [99, 100]
	FAM134B ATL; RTN3L	Intervertebral disc-degeneration Alzheimer's disease	[102] [91]
Cancer	SEC62 FAM134B	Cervical spondylosis myelopathy Hepatocellular carcinoma	[101] [103, 105]
	SEC62	Non-small-cell Lung Cancer, Prostatic carcinoma, Thyroid carcinoma	[107]
	SEC62	Colorectal cancer	[108]
	SEC62	Gastric cancer	[21, 109]
Metabolic disease	SQSTM1 FAM134B FAM134B	alpha-1-antitrypsin deficiency alpha-1-antitrypsin deficiency Diabetic kidney disease	[68] [17] [118]
	RTN3	Obesity	[121]
Cardiovascular disease	CCPG1 SEC62; RTN3L FAM134B FAM134B	Cardiomyopathy Diabetic cardiomyopathy Sepsis Myocardial infarction	[124] [127, 128] [125] [126]
Infections and inflammation	FAM134B FAM134B FAM134B; SEC62 FAM134B UBAC2	Cardiac hypertrophy EBOV Viral infections <i>Salmonella</i> Typhimurium Inflammation	[130] [131] [132–134] [78] [71]

HSAM II hereditary sensory and autonomic neuropathy type II, PD Parkinson's disease, AE acquired epilepsy, IDD intervertebral disc-degeneration, AD Alzheimer's disease, CSM cervical spondylosis myelopathy, HCC hepatocellular carcinoma, NSCLC non-small-cell lung cancer, PC prostatic carcinoma, THCA thyroid carcinoma, CRC colorectal cancer, ATD alpha-1-antitrypsin deficiency, DKD diabetic kidney disease, DCM diabetic cardiomyopathy, EBOV Ebola virus.

Following AD, Parkinson's disease (PD) ranks as the second leading neurodegenerative disorder worldwide. PD is associated with the degenerative death of nigrostriatal dopaminergic neurons. In PD, accumulation of α -synuclein within the ER triggers ER stress, increases reactive oxygen species (ROS), and disrupts calcium and redox balance, ultimately activating the UPR and leading to neuronal death [96, 97]. FAM134B-regulated ER-phagy is crucial for α -synuclein degradation, and enhancing this process confers neuroprotection to dopaminergic neurons in PD models. Therefore, targeting ER-phagy to accelerate α -synuclein removal may offer a promising treatment strategy for Parkinson's disease [98].

In acquired epilepsy (AE), ER stress and autophagy are induced along with calcium dysregulation and ROS accumulation. Over-expression of FAM134B alleviates ER stress, restores ER function, and protects neurons by promoting ER-phagy and reducing ROS and ER Ca^{2+} release [99]. Another study found that AE dysregulated Ca^{2+} homeostasis by increasing the expression of calcium transport-related proteins such as inositol 1,4,5-trisphosphate receptor (IP3R) in mitochondrial-associated ER membranes (MAMs), while FAM134B-mediated ER-phagy attenuated AE-induced apoptosis in hippocampal neurons. Mechanistically, FAM134B-mediated ER-phagy may decrease IP3R expression in MAMs, increase ER Ca^{2+} levels, and decrease mitochondrial Ca^{2+} levels, thereby inhibiting mitochondria-dependent apoptosis and attenuating AE-induced neuronal injury [100].

Cervical spondylotic myelopathy (CSM) is characterized by progressive damage to the cervical spinal cord caused by degeneration of the cervical intervertebral discs. The lipophilic nature of the antioxidant melatonin facilitates its entry into the central nervous system and its accumulation in the nucleus, which is therapeutically useful in acute spinal cord injury. Melatonin has been shown to promote ER-phagy and alleviate ER stress by increasing the expression of SEC62, thereby restoring ER homeostasis and protecting neurons [101]. In intervertebral disc-degeneration (IDD), aberrant apoptosis of nucleus pulposus (NP) cells, the basic functional unit of NP tissue, and concomitant

damage to senescent cells are important pathological processes. Under conditions of nutrient deprivation, the expression of O-GlcNAc transferase (OGT) is increased in degenerating NP tissue and NP cells. OGT directly interacts with the FAM134B protein and exerts a cytoprotective effect by inhibiting ubiquitin-mediated degradation, thereby increasing the stability of FAM134B and enhancing FAM134B-mediated ER-phagy [102] (Fig. 4).

In summary, ER-phagy plays an important role in removing misfolded proteins and responding to ER stress. Given that many neurological and neurodegenerative diseases are characterized by protein misfolding and disrupted ER homeostasis, targeting ER-phagy represents a promising therapeutic strategy for future interventions in neurodegenerative disorders.

Cancer

Cancer remains one of the leading causes of death worldwide, resulting from an imbalance between oncogenes and tumor suppressor genes. Both ER stress and ER-phagy are involved in various stages of cancer development. The role of ER-phagy in tumorigenesis is multifaceted and appears to be influenced by factors such as cancer type, progression stage, and the tumor microenvironment. On one hand, ER-phagy attenuates excessive ER stress, thereby supporting cancer cell proliferation and survival. On the other hand, overactivation of ER-phagy can lead to the formation of numerous autophagosomes, accelerate ER degradation and disrupt ER homeostasis, thereby triggering cancer cell death. Thus, regulating ER-phagy through the modulation of ER-phagy receptor expression may offer a potential strategy to inhibit cancer metastasis and progression.

FAM134B has been found to be highly expressed in hepatocellular carcinoma (HCC), where it promotes tumor development by regulating the Akt signaling pathway to enhance proliferation, invasion and metastasis of HCC cells [103]. Knockdown of FAM134B significantly induced apoptosis of HCC cells and effectively inhibited their migration and invasion [104]. Since FAM134B regulates ER turnover, downregulation of its expression may affect ER-phagy and interfere with protein processing and

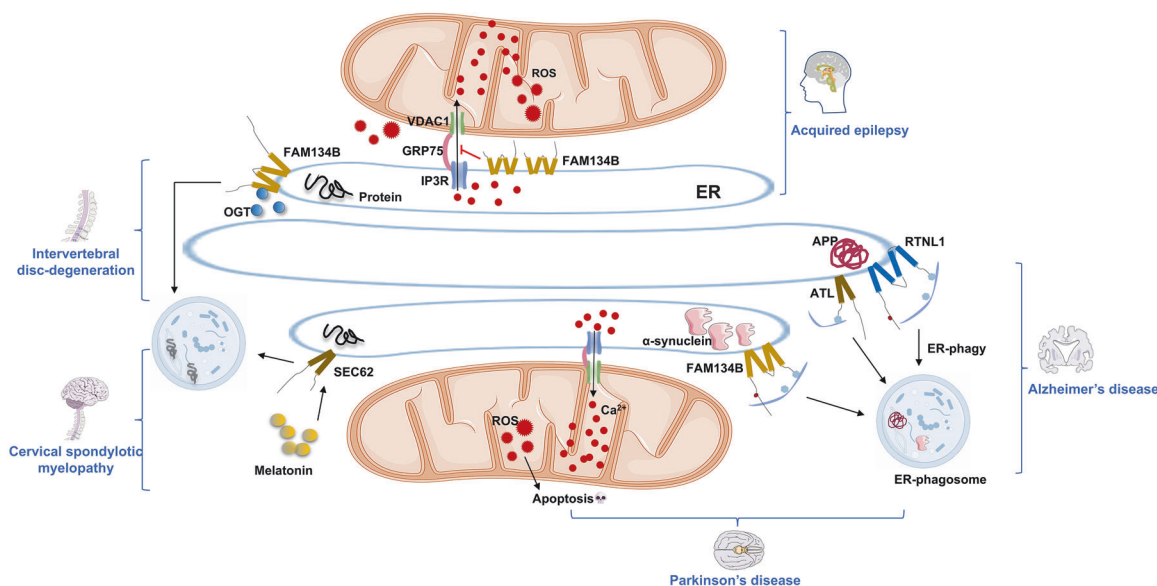


Fig. 4 ER-phagy receptors are implicated in the pathogenesis of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), acquired epilepsy (AE), cervical spondylotic myelopathy (CSM) and intervertebral disc-degeneration (IDD). In AD, increased ATL or RTNL1 receptor levels enhance ER-phagy, promoting the degradation of APP to reduce $\text{A}\beta$ production and associated toxicity. In PD, FAM134B-mediated ER-phagy degrades α -synuclein, protecting dopaminergic neurons. In AE, FAM134B overexpression attenuates ER Ca^{2+} release and ROS production, alleviates ER stress, and restores ER function. In CSM, melatonin upregulates SEC62, promoting ER-phagy to restore ER homeostasis. In IDD, OGT stabilizes FAM134B by inhibiting ubiquitin-mediated degradation, enhancing FAM134B-dependent ER-phagy. VDAC1 voltage-dependent anion channel, GRP75 glucose-regulated protein 75, IP3R inositol 1,4,5-trisphosphate receptor, ROS reactive oxygen species, OGT O-GlcNAc transferase.

trafficking, thereby effectively inhibiting HCC cell proliferation and metastasis. However, there are contrary reports showing that the compound Z36 induces ER stress by upregulating ER stress-related proteins such as IRE1, PERK, CHOP, and GRP78 in HeLa cells. FAM134B-mediated ER-phagy is a requisite for Z36-induced ER stress. Z36 upregulates FAM134B expression, promotes LC3-I to LC3-II conversion, triggers excessive ER-phagy, disrupts cellular homeostasis and ultimately leads to cancer cell death. Mechanistically, FAM134B binds via its C-terminal cytoplasmic domain to stromal interaction molecule 1 (STIM1), an ER Ca^{2+} sensor protein that mediates the G1 to S phase transition. Knockdown of FAM134B reduces the ER-to-autolysosome transport and degradation of STIM1, thereby accelerating the G1-to-S transition, suggesting that FAM134B may inhibit cell proliferation by degrading STIM1 through ER-phagy [105]. Thus, the role of FAM134B-mediated ER-phagy in cancer is complex and multifaceted—it can promote tumor progression or induce apoptosis depending on the cellular context and regulatory mechanisms [106].

In non-small cell lung cancer (NSCLC), prostate cancer and thyroid cancer, enhanced SEC62-mediated ER-phagy increases cancer cell tolerance to ER stress and enhances metastatic and invasive potential, which is associated with poorer patient outcomes [107]. In human colorectal cancer (CRC), SEC62 activates the β -catenin signaling pathway, thereby increasing cancer stemness and attenuating chemosensitivity of CRC. Conversely, SEC62 deletion enhances drug sensitivity and reduces stemness in CRC cells [108]. SEC62 expression is upregulated in gastric cancer, where it induces autophagy via the UPR-related PERK/ATF4 pathway and binds to LC3II during the FIP200/Beclin-1/Atg5 complex-mediated restoration process, regulating the balance between matrix metalloproteinases (MMP)2/9 and tissue inhibitor of metalloproteinases (TIMP)-1 to promote metastasis [21, 109]. Therefore, SEC62 inhibitors that block ER-phagy could be a potential therapeutic strategy for treating solid tumors with elevated SEC62 expression or for overcoming chemotherapy resistance.

In contrast, RTN3 and TEX264 are expressed at low levels in cancer cells. RTN3 expression is significantly reduced in HCC compared to normal hepatocytes. It was found that RTN3 was able

to interact with CHK2, recruiting it to the ER in an ER calcium-dependent manner and promoting its activation. Activated CHK2 then phosphorylates p53, inducing growth arrest and apoptosis. Therefore, RTN3 may be a novel tumor suppressor in HCC [110]. Similarly, TEX264 expression is decreased in clear cell renal cell carcinoma [111]. TEX264 participates in the repair of TOP1cc—a cytotoxic lesion targeted by anticancer agents such as camptothecin—through cooperation with the p97 ATPase and the SPRTN metalloproteinase [51, 56]. However, the relationship between the anti-cancer effects of RTN3 and TEX264 and their functions in ER-phagy needs to be further investigated (Fig. 5).

Metabolic disease

Metabolic diseases such as diabetes mellitus and fatty liver disease are often associated with severe ER stress and ER-phagy dysfunction. Therefore, promoting ER-phagy may ameliorate ER stress and delay the progression of metabolic diseases.

The function of alpha-1-antitrypsin (AT) is to protect organs and normal cells from protease damage and to maintain homeostasis of the internal environment. A point mutation substituting glutamic acid at position 342 with lysine produces a mutant protein known as ATZ. When expressed at high levels, mutant ATZ tends to misfold and aggregate, accumulating in the ER and hindering its degradation [112]. This process triggers UPR activation and causes ER stress, ultimately leading to alpha-1-antitrypsin deficiency (ATD). ATD further exacerbates apoptosis and hepatocyte damage. In mammalian cells, SQSTM1 and TRIM13 have been shown to bind to and degrade ATZ aggregates via ER-phagy, thereby reducing ER stress induced by ATZ aggregation and lowering the risk of liver injury and HCC [68]. Additionally, ATZ aggregates can be removed through the ERLAD pathway mediated by both FAM134B and calnexin (CNX) [17]. ER stress also contributes to acetaminophen (APAP)-mediated hepatotoxicity in APAP-induced acute-liver injury [113]. In APAP-treated mice, TEX264-mediated ER-phagy was shown to attenuate ER stress induced by APAP overdose. Glycycomarin (GCM) enhances TEX264-mediated ER-phagy, thereby inhibiting ER stress, alleviating APAP-induced liver injury, and promoting liver regeneration [114]. In addition, p62-dependent ER-phagy and mitophagy may play key roles in the clearance of cytotoxic substances. The p62

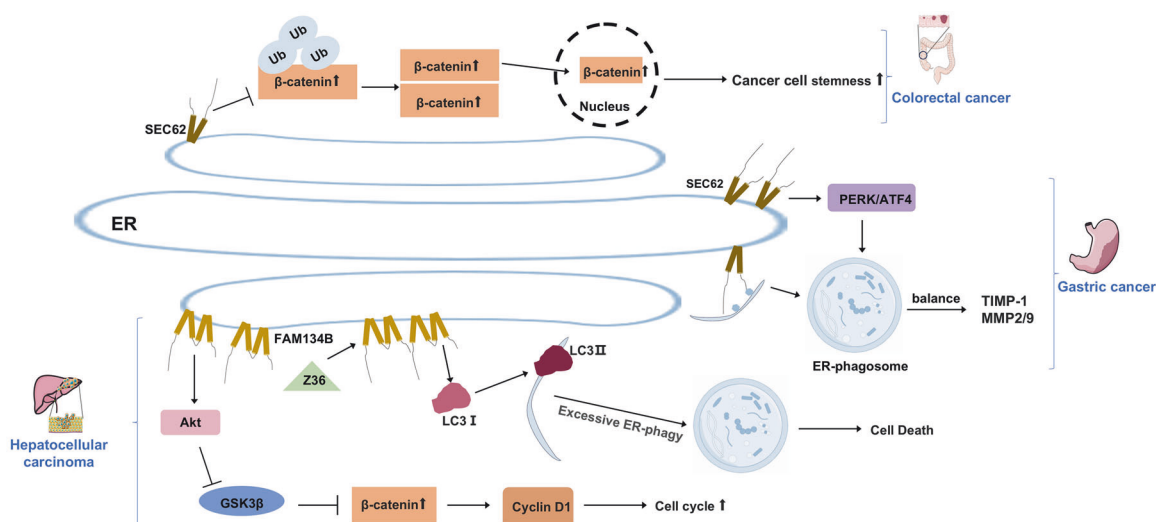


Fig. 5 ER-phagy receptors are implicated in the pathogenesis of cancers, including colorectal cancer (CRC), hepatocellular carcinoma (HCC) and gastric cancer. In HCC, FAM134B is highly expressed and promotes HCC progression by activating the Akt signaling pathway, enhancing cell proliferation, invasion, and metastasis. The compound Z36 upregulates FAM134B, increases LC3-I to LC3-II conversion, induces excessive ER-phagy, and leads to cancer cell death. In CRC, SEC62 activates β -catenin signaling, increasing cancer stemness and reducing chemosensitivity. In gastric cancer, SEC62 activates autophagy via the UPR-related PERK/ATF4 pathway, disrupting the MMP2/9 - TIMP-1 balance to promote metastasis. ATF4 activating transcription factor, PERK Protein kinase R-like endoplasmic reticulum kinase, MMP2/9 matrix metalloproteinases 2/9, TIMP-1 tissue inhibitor of metalloproteinases-1, Akt protein kinase B, GSK3 β Glycogen synthase kinase 3 β , Ub Ubiquitination

agonist YTK-2250 attenuates APAP-induced liver injury by promoting the clearance of dysfunctional ER and mitochondria [115]. Similarly, CCPG1-mediated ER-phagy prevents pancreatitis by maintaining pancreatic homeostasis *in vivo* through timely clearance of insoluble proteins from the ER [56], while piperine reduces ER stress and attenuates pancreatic injury by enhancing CCPG1-dependent ER-phagy [116].

Diabetic kidney disease (DKD) is the primary cause of end-stage renal disease. In DKD patients and animal models, the expression of RETREG1/FAM134B is decreased in renal tubular cells. FAM134B exerts a protective effect against tubular injury by restoring ER-phagy and mitigating ER stress in tubular cells during DKD [117]. Phosphofurin acidic cluster sorting protein 2 (PACS-2), a membrane trafficking protein, maintains the integrity of MAMs within renal tubular epithelium, thereby alleviating ER stress and slowing DKD progression in mice [118]. Interestingly, PACS-2 also promotes nuclear translocation of the transcription factor TFEB, upregulates FAM134B transcription and expression, and activates ER-phagy, thus playing a protective role in diabetic tubulointerstitial injury [119].

Obesity and its complications are major risk factors for many chronic diseases that represent leading causes of mortality in both adults and children. Increased RTN3 expression has been found in obese and hypertriglyceridemic patients. CCAAT/enhancer-binding protein α (C/EBP α), a direct transcription factor of RTN3, is significantly upregulated under lipid overload conditions and binds directly to the promoter region of RTN3 to increase its expression [120]. RTN3 may be a key molecule in lipid metabolism. Elevated RTN3 expression enhances its interaction with heat shock protein family A member 5 (HSPA5), reducing HSPA5 activity and stabilizing the SREBP-SCAP complex (sterol regulatory element-binding protein and SREBP cleavage-activating protein), thereby increasing triglyceride accumulation [121]. RTN3 may directly interact with fatty acid binding protein 5 (FABP5) to facilitate the targeted delivery of fatty acids to the ER, thereby promoting lipid droplet formation through a diacylglycerol O-acyltransferase 2 (DGAT2)-dependent mechanism [120]. However, whether the role of RTN3 in regulating lipid metabolism is related to ER-phagy requires further investigation. Interestingly, RTN3L-mediated ER-phagy has been shown to extensively degrade misfolded

hormone precursor proteins accumulated in the ER, ensuring proinsulin remains in a soluble form for proper processing and secretion [122, 123] (Fig. 6).

Cardiovascular disease

CVDs remain a leading cause of morbidity and mortality worldwide, posing a major global health challenge. ER-phagy plays an important regulatory role in maintaining cardiomyocyte metabolism and survival. Under physiological conditions, basal ER-phagy activity may be protective, whereas excessive activation may lead to detrimental effects.

CCPG1-mediated ER-phagy exerts a protective function by mitigating cardiomyocyte injury in doxorubicin (DOX)-induced cardiomyopathy. Mechanistically, phosphorylation of CCPG1 at serine 104 enhances its binding affinity to FIP200. Tank-binding kinase 1 (TBK1), a serine/threonine protein kinase, phosphorylates CCPG1, thereby promoting its interaction with FIP200 and facilitating ER-phagy initiation [124]. Sepsis is a systemic inflammatory response syndrome caused by infection. In sepsis, excessive production of proinflammatory cytokines such as TNF- α , IL-6, and IL-8 contributes to myocardial dysfunction. Increased expression of FAM134B and autophagy-related proteins LC3 I/II induces ER-phagy, which reduces the production of these inflammatory factors (TNF- α , IL-6, IL-8), thereby attenuating both the inflammatory response and myocardial dysfunction, and protecting myocardial tissue from sepsis-induced injury [125]. FAM134B-mediated ER-phagy is upregulated following myocardial infarction (MI). Mechanistically, the E3 ubiquitin ligase AMFR primarily catalyzes K27-linked and K33-linked ubiquitination of FAM134B. This modification enhances ER-phagy flux while suppressing the phosphorylation of downstream mTORC1 targets, including S6K1 and 4E-BP. These findings highlight the therapeutic potential of ER-phagy in suppressing cardiac fibrosis post-MI [126].

However, excessive ER-phagy can exacerbate cardiac damage. Diabetic cardiomyopathy (DCM) is one of the causes of heart failure in diabetic patients, and ER stress is considered an important pathological mechanism of DCM. Under hyperglycemic conditions, ER stress elevates the levels of CHOP, caspase-12, and calnexin, leading to apoptosis. Elevated expression of SEC62 and RTN3L enhances ER-phagy in cardiomyocytes under high-glucose

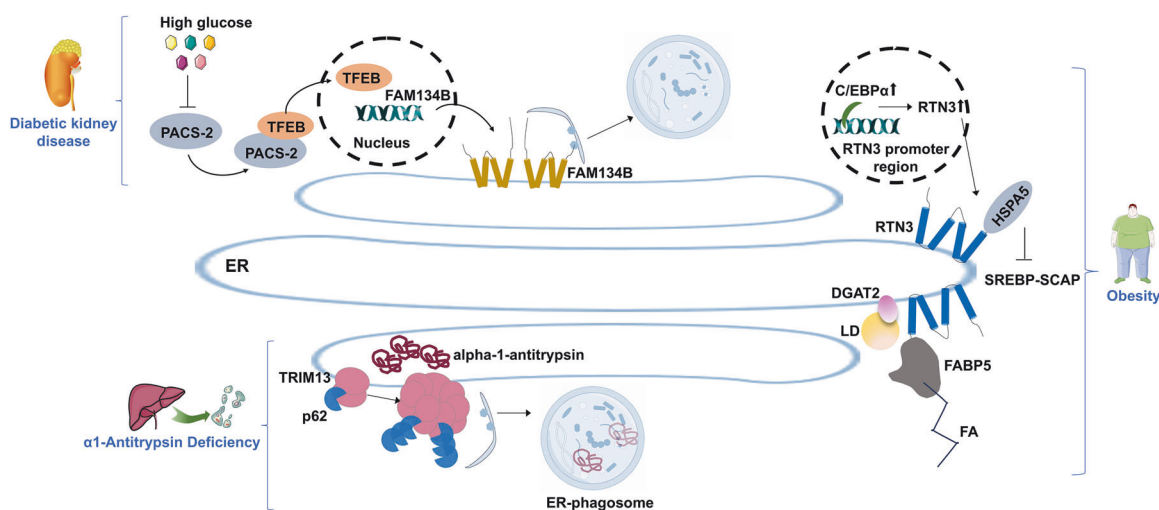


Fig. 6 ER-phagy receptors are implicated in the pathogenesis of metabolic disease, including alpha-1-antitrypsin deficiency (ATD), diabetic kidney disease (DKD) and obesity. In ATD, SQSTM1 and TRIM13 degrade ATZ aggregates via ER-phagy, reducing ER stress and lowering risk of liver injury and hepatocellular carcinoma. In DKD, PACS-2 promotes TFEB nuclear translocation, upregulates FAM134B and activates ER-phagy. In obesity, increased RTN3 expression binds HSPA5, destabilizing the SREBP-SCAP complex and increasing triglycerides (TGs). RTN3 also directly interacts with FABP5 to promote fatty acid transport to the ER, promoting DGAT2-dependent LD biogenesis. PACS-2 Phosphofurin acidic cluster sorting protein 2, C/EBP α CCAAT/enhancer binding protein α , HSPA5 heat shock protein family A member 5, SREBP sterol regulatory element-binding protein, SCAP SREBP cleavage-activating protein, FABP5 fatty acid binding protein 5, DGAT2 diacylglycerol O-acyltransferase 2, LD lipid droplet.

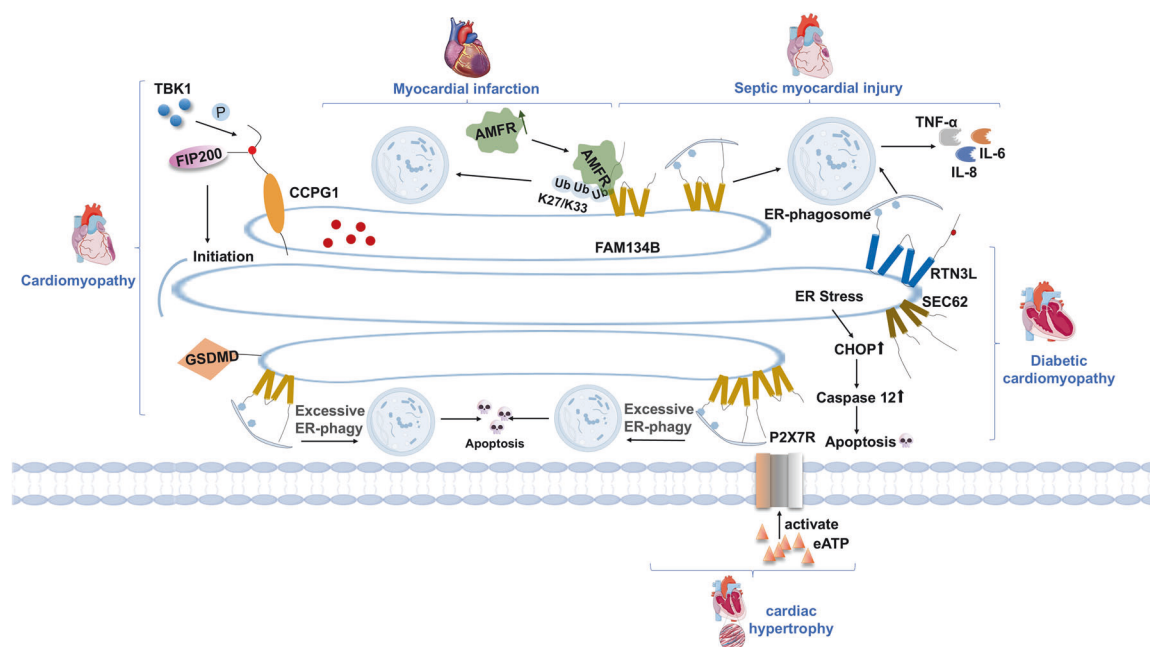


Fig. 7 ER-phagy receptors are implicated in the pathogenesis of cardiovascular diseases including cardiomyopathy, septic myocardial injury, diabetic cardiomyopathy, cardiac hypertrophy and myocardial infarction (MI). In cardiomyopathy, TBK1 phosphorylates CCPG1, enhancing its interaction with FIP200 to initiate ER-phagy. GSDMD binds to the ER via its N-terminus, activating FAM134B to promote ER-phagy and apoptosis, thereby exacerbating cardiac injury. In septic myocardial injury, increased FAM134B expression induces ER-phagy, reducing the production of inflammatory cytokines (TNF- α , IL-6 and IL-8). In diabetic cardiomyopathy, elevated SEC62 and RTN3L levels enhance ER-phagy in cardiomyocytes. In cardiac hypertrophy, eATP activates the P2X7 receptor, upregulates FAM134B expression, and promotes FAM134B-dependent ER-phagy, contributing to disease progression. In myocardial infarction, the E3 ubiquitin ligase AMFR catalyzes K27- and K33-linked ubiquitination of FAM134B, enhancing ER-phagy flux, thereby mitigating cardiac fibrosis. AMFR autocrine motility factor receptor, TBK1 tank-binding kinase 1, GSDMD Gasdermin D, P2X7 purinergic ligand-gated ion channel 7, CHOP C/EBP-homologous protein, Caspase 12 cysteinyl aspartate specific proteinase 12, TNF- α tumor necrosis factor, IL-6 interleukin-6, IL-8 interleukin-8.

conditions, whereas chlorogenic acid (CA) reverses ER-phagy overactivation and inhibits ER stress-induced apoptosis, effectively counteracting DCM [127, 128].

It has also been shown that the expression of gasdermin D (GSDMD), a protein closely associated with pyroptosis, is upregulated in DOX-induced cardiotoxicity. GSDMD exacerbates cardiac injury by binding to the ER via its N-terminus, activating FAM134B to promote ER-phagy and apoptosis [129]. In cardiac hypertrophy, autophagy levels are significantly elevated, and sustained autophagy activation may exacerbate cardiac hypertrophy. Apelin-13 stimulates pannexin-1 hemichannel opening to release intracellular ATP, which activates the purinergic ligand-gated ion channel 7 (P2X7) receptor, upregulates FAM134B expression, and promotes FAM134B-dependent ER-phagy, contributing to the pathology of cardiac hypertrophy [130]. Therefore, inhibition of the pannexin-1/P2X7 axis and FAM134B-dependent excessive ER-phagy may provide a new therapeutic strategy for cardiac hypertrophy (Fig. 7).

Infection and inflammatory diseases

ER-phagy plays a vital role in the host defense against various viral and bacterial infections. The Ebola virus (EBOV) is known to cause severe hemorrhagic fever. Viral glycoprotein (GP) facilitates viral entry into host cells, with the ER processing GP from its immature form to a fully glycosylated mature form. FAM134B-mediated ER-phagy has been shown to inhibit EBOV replication by preventing GP maturation [131]. Notably, the host protein CXCR4 (C-X-C motif chemokine receptor 4) exhibits a dual role during EBOV infection, promoting viral entry while also facilitating FAM134B-dependent ER-phagic degradation of excess viral GP [117]. Furthermore, FAM134B-mediated ER-phagy restricts the replication of flaviviruses such as Dengue virus (DENV) and Zika virus (ZIKV), acting

as an antiviral mechanism [132]. Mechanistically, the E3 ubiquitin ligase AMFR mediates the ubiquitination of the viral NS2A protein and binds FAM134B to form the NS2A-FAM134B complex, which is subsequently degraded via AMFR coordination [133]. Additionally, the ubiquitin-conjugating enzyme Ube2g2, a cofactor of the lipid droplet-associated protein ancient ubiquitin-like protein 1 (Aup1). Loss of Ube2g2 results in SEC62 upregulation, triggering SEC62-dependent ER-phagy and suppressing flavivirus replication [134]. Furthermore, the ER also serves as the primary membrane source for the formation of SARS-CoV-2 double-membrane vesicles (DMVs). The viral ORF8 interacts with p62 to form dimers that inhibit ER-phagy by preventing FAM134B and ATL3 from entering these dimers, thereby promoting DMV formation and viral replication [135]. Similarly, *Salmonella typhimurium* inhibits FAM134B oligomerization through its effector SopF to suppress ER-phagy, thereby enhancing bacterial survival and infection [78]. Therefore, understanding the role of ER-phagy and its receptors in human infections could potentially identify novel therapeutic targets for combating infections.

ER-phagy dysfunction is associated with the UPR response, a key factor implicated in the pathogenesis of inflammatory diseases. The novel ER-phagy receptor UBAC2 acts as a negative regulator of inflammation. During inflammation-induced autophagy, microtubule affinity-regulating kinase 2 (MARK2) phosphorylates UBAC2, promoting dimer formation and enhancing its interaction with GABARAP, which accelerates ER-phagy. This process contributes to the maintenance of cellular homeostasis and effectively suppresses the inflammatory response [71]. Despite these advances, current research on ER-phagy in inflammatory diseases remains limited, and future studies are urgently needed to further explore this field and reveal more potential mechanisms and connections (Fig. 8).

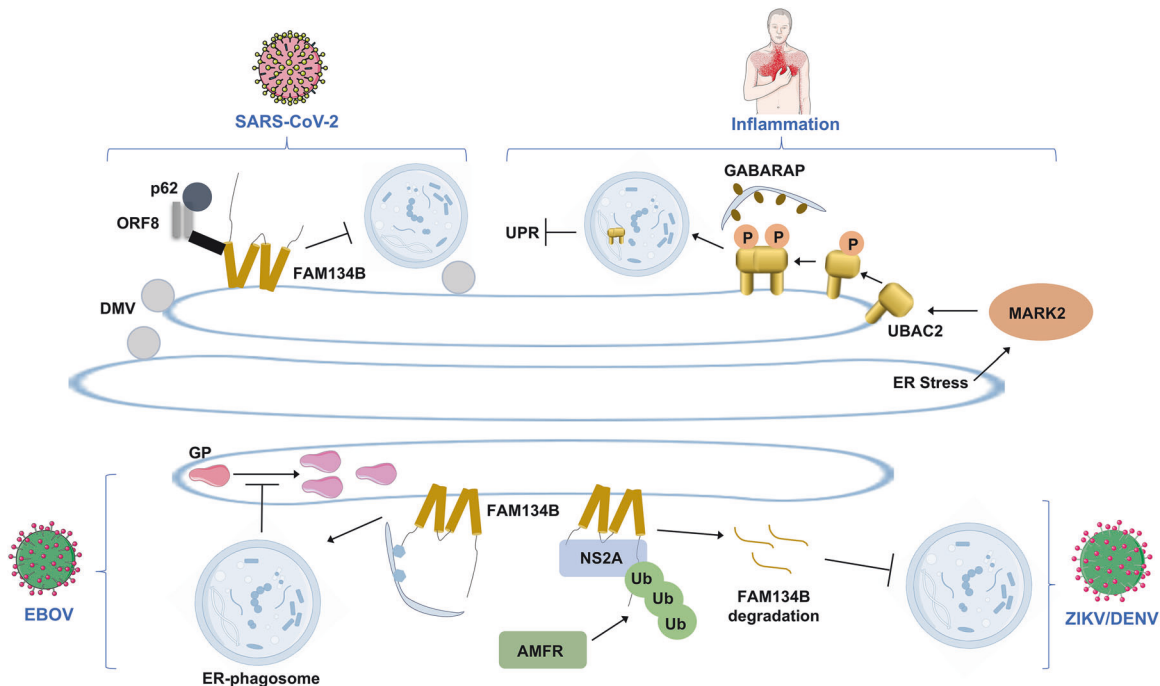


Fig. 8 Roles of ER-phagy receptors in inflammatory diseases and infections. Upon inflammatory stimulation, MARK2 phosphorylates UBAC2, promoting its dimerization, which enhances the UBAC2- GABARAP interaction and thereby facilitates ER-phagy. In EBOV infection, FAM134B-dependent ER-phagy inhibits viral replication by blocking GP maturation. In cells infected with ZIKV or DENV, FAM134B-mediated ER-phagy restricts viral replication. Mechanistically, the E3 ubiquitin ligase AMFR ubiquitinates viral NS2A and binds with FAM134B to form the NS2A-FAM134B complex, which is subsequently degraded via AMFR coordination, thereby impeding ER-phagy flux. In SARS-CoV-2 infection, the viral protein ORF8 sequesters p62 into dimers, thereby promoting coronavirus DMVs formation and viral replication. GP glycoprotein, AMFR autocrine motility factor receptor, NS2A nonstructural protein 2A, DMV double- membrane vesicles, ORF8 open reading frame 8, p6 Sequestosome 1, MARK2 microtubule affinity-regulating kinase 2, UBAC2 ubiquitin-associated domain-containing protein 2, GABARAP GABA type A receptor-associated protein. UPR unfolded protein response.

SUMMARY AND PROSPECTS

As one of the major intracellular organelles, ER requires the maintenance of its homeostasis for proper cellular function. ER-phagy selectively mediates the degradation and removal of ER fragments to regulate ER morphology and function, making it one of the key processes for maintaining ER homeostasis. In recent years, the identification of multiple ER-phagy receptors—including FAM134B, RTN3L, TEX264, SEC62 and ATL3—has revealed their significant involvement in neurological disorders, cancer, metabolic diseases, and CVDs. However, the current understanding of ER-phagy remains incomplete. Regarding its association with different diseases, further research is needed to determine which receptors play more important roles in the pathological process, or whether agonists or inhibitors of specific receptors exist. We believe that a deeper understanding of the roles of ER-phagy in diseases will emerge through further studies of ER-phagy receptors and their functions. Most current studies focus on FAM134B-mediated ER-phagy, while the regulatory mechanisms of other ER-phagy receptors, particularly in disease contexts, are less well studied. Future research should focus on conducting in-depth studies on these ER-phagy receptors to elucidate their roles and mechanisms more comprehensively. Additionally, growing evidence reveals that ER-phagy receptors regulate other forms of non-selective and selective autophagy and cellular processes. For example, recent studies show that TEX264 plays a key role in nucleophagy [57]. Moreover, emerging research indicates that ER-phagy receptors can form novel ER-derived structures, such as ER-tubular bodies (ER-TBs) formed by ATL3 and RTN3L, which mediate Golgi-bypassing unconventional protein secretion under stress conditions, revealing non-degradative functions of these receptors beyond quality control [136]. Collectively, these findings

suggest that ER-phagy may be intricately linked with other autophagic and cellular processes, warranting further exploration. ER-phagy also represents a promising therapeutic target. By studying ER-phagy receptors and investigating their regulatory mechanisms, novel therapeutic strategies may be developed for a wide range of diseases, offering great potential for disease prevention and promoting human health.

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ADDITIONAL INFORMATION

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