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Mechanisms and physiological functions of ER-phagy

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The endoplasmic reticulum (ER) is the largest cellular organelle that undergoes constant turnover upon diverse functional demands and cellular signals. Removal of nonfunctional or superfluous subdomains is balanced by the parallel expansion and formation of ER membranes, leading to the dynamic exchange of ER components. In recent years, selective autophagy of the ER, termed ER-phagy, has emerged as a predominant process involved in ER degradation and maintenance of ER homeostasis. Identification of multiple ER-phagy receptors, many with additional ER-shaping functions, paved the way for our molecular understanding of ER turnover in different cells and organs. In this review, we describe the molecular principles underling the physiological functions of ER-phagy in maintaining ER homeostasis via receptor-mediated macroautophagy and elaborate current focus points of the field.

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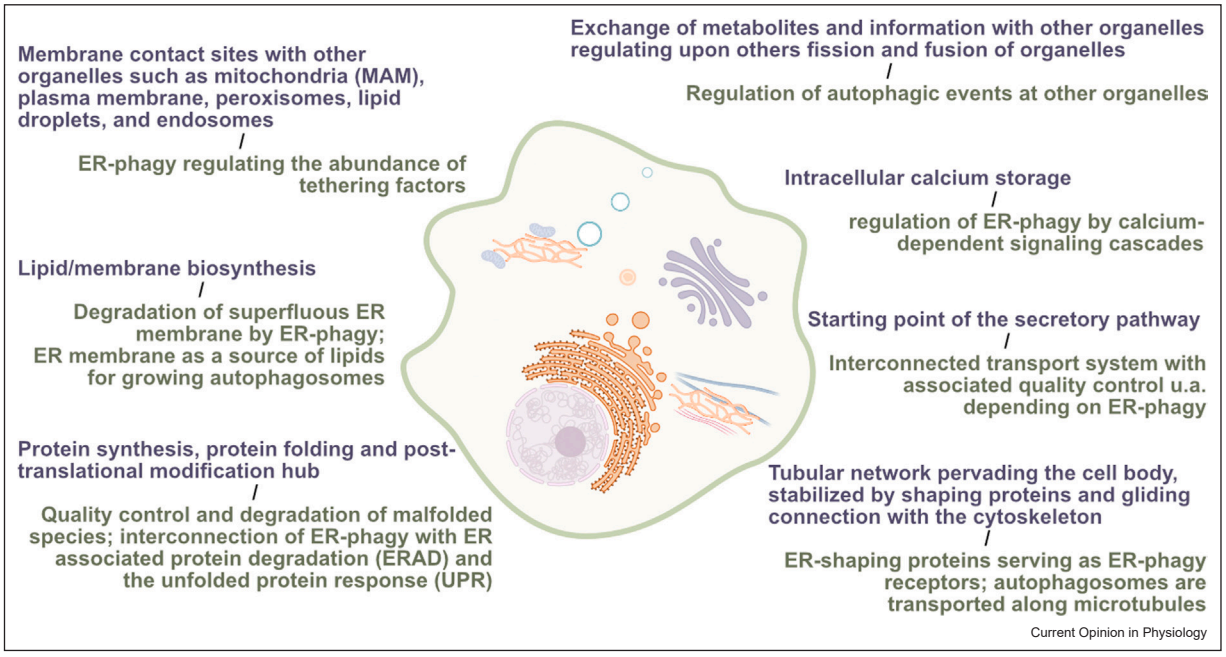
The endoplasmic reticulum (ER) pervades the entire cell body by being centered around the nucleus with sheet-like structures (cisternal ER) that taper into tubular structures (tubular ER) reaching toward the cell periphery. Structural diversity and the adaptability of ER mass in response to altered needs provide the basis for a plethora of important cellular functions. For example, cisternal ER decorated with ribosomes, commonly known as the rough ER, is an important region for protein synthesis, protein quality control, folding, and post-translational modifications, whereas lipids are synthesized at the smooth cisternal ER. The tubular ER serves as an interconnecting web that communicates via physical contact sites with other organelles, including mitochondria (also called mitochondria-associated membranes), plasma membrane, peroxisomes, lipid droplets, early and late endosomes, Golgi, and lysosomes [1]. Structurally, the ER network is stabilized by specific ER-shaping proteins as well as gliding tethers with the cytoskeleton [2,3]. Last but not least, the ER is the entry point of the secretory pathway and part of the interwind vesicular transport system of the cell. In order to fulfil these demanding tasks and to reach the most remote parts of the cell, the shape and structure of the ER is fluid and dynamic, and as such, under strict spatiotemporal regulation (Figure 1). Several cellular pathways induce and contribute to this process, including different types of autophagy pathways as well as autophagy-independent pathways such as ER-associated protein degradation (ERAD) and the unfolded protein response (UPR) [4]. In this review, we concentrate on receptor-mediated degradation of the ER via macroautophagy (from now on termed ER-phagy and autophagy for simplicity).

Autophagy is an essential process that sequesters cellular material into double-membrane vesicles (autophagosomes), that are subsequently transported to the lysosome where its content is degraded and recycled [5]. Autophagic membranes are decorated with members of the ubiquitin-like ATG8 protein family fused to the lipid phosphatidylethanolamine. Lipidated ATG8 proteins serve as critical docking points for proteins containing LIR motifs (LC3-interacting region, also called AIM for ATG8-interacting motif) or selected UIM motifs (ubiquitin-interacting motif) [6,7]. Interactors of ATG8 with a function in autophagy are divided into autophagy adaptors (function in regulation and synthesis) and autophagy receptors (function in cargo recruitment and co-delivery to the lysosome), the latter being essential to facilitate the selective sequestration and degradation of specific cargo by linking it to autophagic membrane. Selective autophagy pathways are named by their cargo, resulting in a continuously growing list that includes mitophagy (mitochondria), xenophagy (bacteria), lipophagy (lipid droplets), ER-phagy (endoplasmic reticulum), and all the rest of it.

Autophagy of the endoplasmic reticulum maintains cellular homeostasis by controlling endoplasmic reticulum structure and functions

Degradation of the ER through autophagy (ER-phagy) provides a powerful mechanism to timely deliver ER

Figure 1

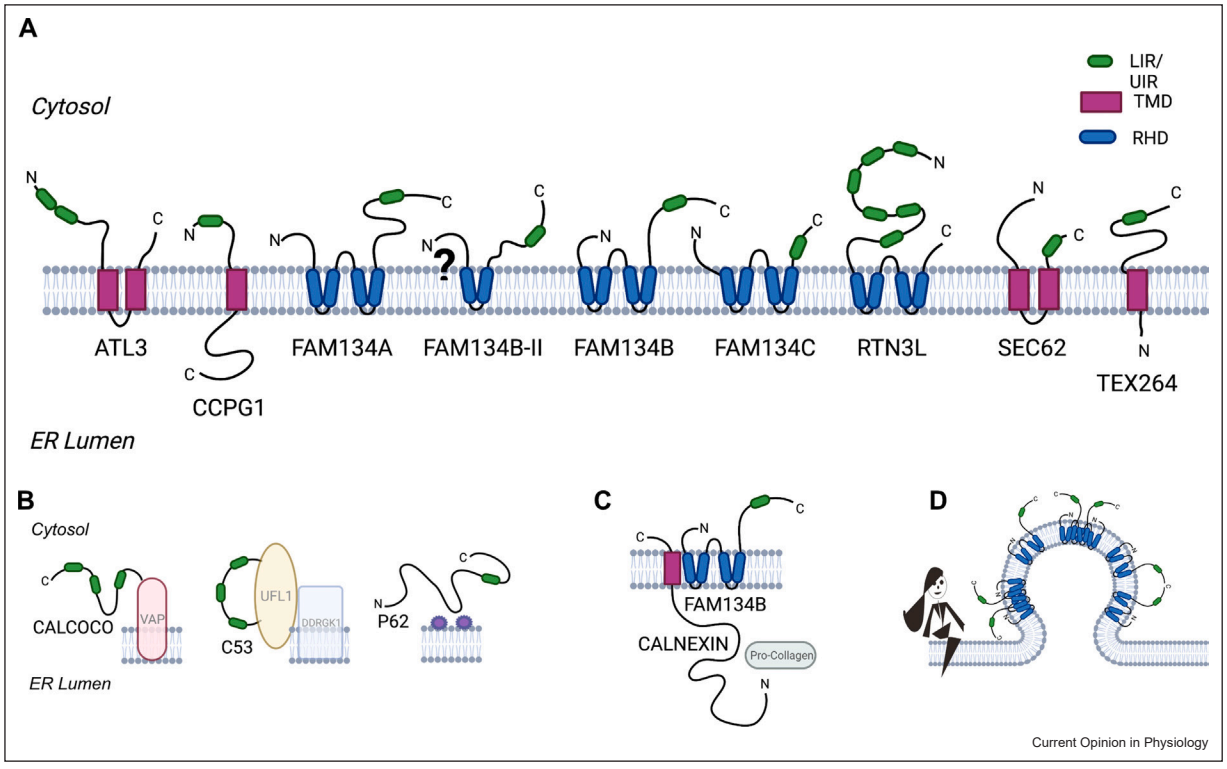


Several physiological properties and functions of the ER are maintained by or connected with autophagic events. Blue text: physiological property or function of the ER; Green text: correlating connection with autophagic events.

membranes and lumen components to the lysosome for degradation. This may be needed under stress conditions, when nutrients are short, or a large number of dysfunctional proteins have to be removed, for example, after high levels of oxidative stress. It is also necessary to keep the ER in a tissue-specific, functional state. For example, pancreatic cells specialized in secretion and skeletal muscle cells certainly depend on different biological functions of the ER. In these cases, specific ER-phagy pathways in concert with transcriptional profiles are either known or predicted to shape the ER into a highly specialized machinery. The ER-phagy process is complex and demanding for several reasons: i) the ER proteome is a mixture of soluble (ER lumen) and membrane-embedded proteins, ii) the ER membrane restricts cytosolic-regulatory factors and signaling cascades to directly act on ER-luminal proteins (and vice versa), and iii) the portion of ER to be degraded needs to be labeled and separated from the continuous network (vesiculation/fragmentation).

The existence of ER-phagy receptors helps to overcome these challenges. Nine membrane-bound ER-phagy receptors have been identified in mammals so far and most likely there are more to come (Figure 2a) [8–15]. Each ER-phagy receptor carries a cytosolic domain with one or more LIR motifs and is therefore able to link their cargo with autophagic membranes. Via their trans- or intramembrane domains, receptors are anchored within the ER (in this case the cargo to be degraded) and, upon specific stimuli, they are delivered together with defined ER portions to the lysosome for degradation. (Most) ER-phagy receptors have an additional, autophagy-independent function, which supports ER homeostasis in one or another way. FAM134A, FAM134B, FAM134C, as well as RTN3L carry a reticulon homology domain (RHD) that localizes at high-curvature membranes and together with other shaping proteins supports the ER structure (Figure 2) [2,16]. TEX264 and ATL3 are preferentially located at three-way junctions. Moreover, with its GTPase activity, ATL3 is directly involved in the formation of the three-way junctions and in concert with RTN proteins fine-tunes tubular ER structure. SEC62 is part of the translocon complex, and as such, has an important function in the import of newly synthesized proteins into the ER, while CCPG1 has been originally characterized as a regulatory scaffold protein for Rho signaling complexes. Evolutionary, these additional features may be the reason why these specific proteins have become ER-phagy receptors and why there are so many different receptors present in a single organelle: the respective autophagy-independent functions will localize the ER-phagy receptor to a specific suborganelle structure or lead to tissue-specific expression. In this way, activation of its autophagic function will lead to the turnover of a specific ER substructure and thereby support the required specificity within ER-phagy pathways. Therefore, it is very likely that each

Figure 2



ER-phagy receptors: key players yet to be understood. Schematic representation of **(a)** the nine membrane ER-phagy receptors in mammals characterized so far; **(b)** identified mammalian cytosolic ER-phagy receptors; **(c)** the function of co-receptors in ER-phagy; and **(d)** the clustering and membrane-shaping effect of RHD-containing ER-phagy receptors.

subdomain and function of the ER has its own, dedicated ER-phagy receptor that is switched on or off upon regulatory triggers.

In accordance with the central function of the ER and the importance of its maintenance, misregulation of ER-phagy has a serious impact on cellular homeostasis and on an organismal level is the cause of disease. Some mutations in and disturbed levels of known ER-phagy receptors have been linked to human diseases [17–21]. The organ-specific dysfunctions of autophagy defects in general include neurodegenerative, cardiovascular, and musculoskeletal diseases as well as ocular, pulmonary, hepatic, renal, and reproductive disorders. At a systemic level, autophagy is involved in cancer development, immune and autoimmune disorders, as well as metabolic syndromes [22]. In many cases, however, it is not yet clear which (selective) autophagy pathway may contribute to a disease. Time will tell how many links between defective ER-phagy and human diseases there are still to be discovered.

The modular design of ER-phagy receptors

Cargo receptors are proteins that bridge the targeted cargo with autophagy machinery and how ER-phagy receptors provide certain substrate specificity was just discussed. But is this enough? For the majority of ER-phagy receptors, cargo binding seems to be an intrinsic feature accomplished by transmembrane domains and permanent ER localization. However, also soluble ER-phagy receptors have been described (Figure 2b) [23–25] and ER localization, even at specific substructures of the ER, may be insufficient to select specific cargo.

Surprisingly, most known ER-phagy receptors lack a large ER-luminal domain, a feature so far only found in CCPG1. CCPG1 also carries a FIP200-binding domain, which is important for its function [4,43]. SEC62 and TEX264 reach into the ER lumen with a short stretch and FAM134B-2 may harbor a short luminal domain (Figure 2a), however, this has only been suggested and FAM134B-2′s precise structural orientation has not yet experimentally been proven. Selective degradation of ER-luminal substrates therefore requires a co-receptor/co-receptor complex with a functional luminal domain binding the cargo and presumably a TM domain to interact with the receptor carrying the LIR motif (Figure 2c). In a few cases, co-receptors are known, for example, Calnexin supporting the degradation of aggregated pro-

collagen, PGRMC1 for misfolded prohormones, and BiP mediating ER-phagy under hypoxic stress [13,26–29]. However, in the majority of cases, the direct link between the ER-phagy receptor and its substrate is rather unclear, which demands the identification and characterization of yet-unknown co-receptors to complete our understanding of this selective process. A mode-of-action, including co-receptors, may also be the case for membrane substrates. Mechanistically, the division of the dual functions of an autophagy receptor (interaction with ATG8 and cargo binding) onto two distinct proteins multiplies the substrate spectrum as well as the application and regulation range. From the ubiquitin field, we know a similar principle: cullin ring ligases have a comparable modularity, utilizing a specific protein class to select substrates and link them to the core ligase via a conserved interaction surface. In the field of ER-phagy, a broader range of co-receptors and subsequently a binding surface — potentially hidden in the membrane domains of known ER-phagy receptors — remains to be revealed.

How are multifunctional ER-phagy receptor complexes regulated?

Our understanding of the variety of possible signals, precise sequence of events, as well as detailed mechanisms is at best patchy. It is, however, clear that during the course of events, substrate-receptor complexes need to cluster and be separated from the ER network by some kind of vesiculation process. The clustering process could be driven in several ways, conceivable by i) clustering of substrates, subsequently leading to substrate-receptor clusters, ii) abundance of receptors, iii) post-translational modifications on substrates or receptors leading to altered biophysical properties, and iv) clustering via interaction with structural proteins. Given the diversity of ER-phagy receptors and substrates, all of these possibilities may play a role in one or the other pathway dependent on their physiological function: are they involved in basal homeostasis or needed for stress response pathways? Is a durable action needed or a rapid response over a short period of time?

In agreement with modular receptor-complex formation, ER-phagy receptors can switch between autophagy-dependent and -independent function, as well as their mode-of-action based on (temporal) cellular needs and stresses (RTN3 as an example: [14,30–34]). A switch may be triggered by pleiotropic signals originating from outside the ER or ER-centric signals (for detailed list of current knowledge, see section 3.3 in [4]).

Abundance of receptors certainly impacts their activity [32,35,36] and local clustering of RHD-containing ER-phagy receptors is thought to induce and promote the vesiculation process [37]. Additional post-translational modifications (such as phosphorylation or ubiquitination) on receptors, co-receptors, and/or substrates may promote local clustering by changing intrinsic properties, promoting protein–protein interactions, recruiting cage-forming coats, or inducing phase separation [13,27,38–43]. In addition, release (or change) of the ER from its tethers to the cytoskeleton and/or organelle-contact sites may change the dynamics of the ER structure and thereby foster vesiculation/fragmentation events [44,45]. Last but not least, (local) lipid composition and state as well as lipid modifications can impact clustering of receptors, co-receptors, and substrates [46–49].

Future outlook

In order to really understand ER-phagy, we depend on fundamental knowledge of basal ER-phagy pathways as well as physiologically relevant triggers apart from starvation. Therefore, technological developments and improvements leading to increased sensitivity of assays measuring changes in ER properties as well as ER-phagy are needed. Such developments may also help to identify/specify a broader range of co-receptors acting in concert with known and yet-unknown ER-phagy receptors, thereby deepening our mechanistical understanding of the process. To avoid misunderstandings or reports of seemingly conflicting findings on one ER-phagy receptor, the nomenclature or standard way of description may need refinement. For example, the well-studied ER-phagy receptor FAM134B may play different roles, depending on available and bound co-receptors. As such, the field may refer by default to ER-phagy receptor complexes (such as $FAM134B^{CNX}$, $C53^{UFL1/DDRGK1}$). It will be interesting to follow which co-receptors have been selected by evolution, and if they are bifunctional in respect of acting in connected pathways such as ERAD and the UPR. Last but not least, the development of small molecules to target individual players of the ER-phagy machinery or selectively induce ER-phagy would move the field a great step forward [50].

Conflict of interest statement

PSM and AS jointly wrote the manuscript. The authors declare no conflict of interest.

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