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CELL SCIENCE AT A GLANCE

ER-phagy at a glance

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ABSTRACT

Selective autophagy represents the major quality control mechanism that ensures proper turnover of exhausted or harmful organelles, among them the endoplasmic reticulum (ER), which is fragmented and delivered to the lysosome for degradation via a specific type of autophagy called ER-phagy. The recent discovery of ER-resident proteins that bind to mammalian Atg8 proteins has revealed that the selective elimination of ER involves different receptors that are specific for different ER subdomains or ER stresses. FAM134B (also known as RETREG1) and RTN3 are reticulon-type proteins that are able to remodel the ER network and ensure the basal membrane turnover. SEC62 and CCPG1 are transmembrane ER receptors that function in response to ER stress signals. This task sharing reflects the complexity of the ER in terms of biological functions and morphology. In this Cell Science at a Glance article and the accompanying poster, we summarize the most recent findings about ER-phagy in yeast and in mammalian cells.

KEY WORDS: Autophagy, CCPG1, FAM134B, RTN3, SEC62, Endoplasmic reticulum

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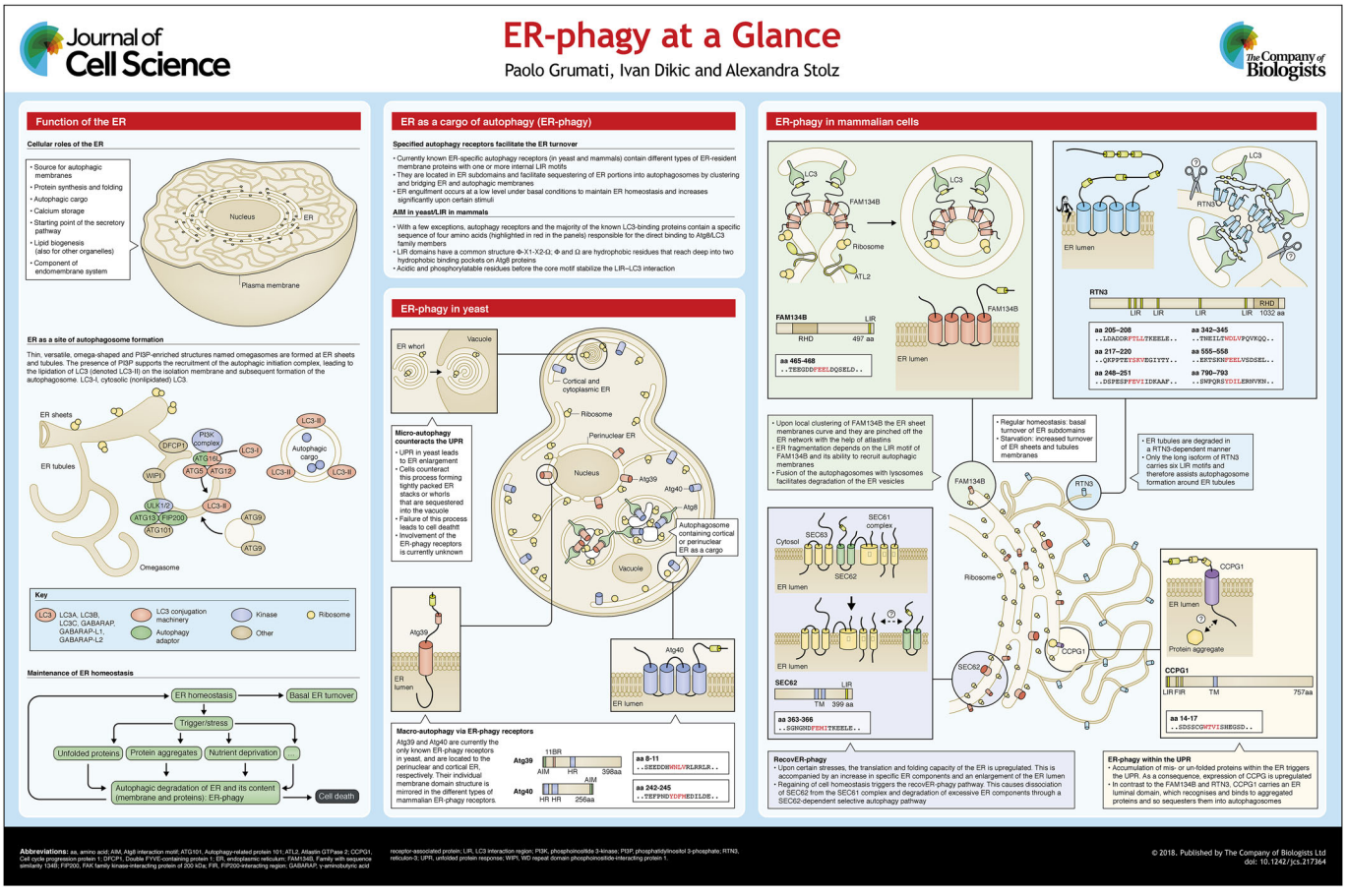
Introduction

The endoplasmic reticulum (ER) is the largest membrane-bound organelle in eukaryotic cells. Its complex morphology, which involves sheets, tubules and matrices (Chen et al., 2013; Friedman and Voeltz, 2011; Nixon-Abell et al., 2016), mirrors its diverse roles in a variety of physiological processes including autophagy (Baumann and Walz, 2001; Lamb et al., 2013; Phillips and Voeltz, 2016). How the elaborate ER network is generated, maintained, disassembled and restored is still a matter of investigation. ER tubules are extremely dynamic and constantly elongate, retract, fuse and slide along the cytoskeleton (Goyal and Blackstone, 2013; Nixon-Abell et al., 2016; Shibata et al., 2009).



Journal of Cell Science (2018) 131, jcs217364. doi:10.1242/jcs.217364

ER sheets are less mobile but still have the capacity to enlarge in response to biological stimuli and shrink back to the original size after the stress is solved (Lu et al., 2009; Wang et al., 2013). The ratio between sheets and tubules, as well as the formation of the ER network is finely regulated by the oligomerization and spatial distribution of specific ER-membrane-bound proteins (Chen et al., 2012; Hu et al., 2011, 2009; Orso et al., 2009; Voeltz et al., 2006) (see poster).

ER function and morphology are intimately linked to autophagy (Lamb et al., 2013). Macro-autophagy (hereafter referred to as autophagy) is a catabolic process that involves the engulfment of cellular material by a double-membraned structure, the phagophore, which eventually closes to form a vesicle called the autophagosome that sequesters the cargo inside. The autophagosome then fuses with the lysosome to degrade the cargo. Of note, two other types of autophagy have been described: micro-autophagy and chaperone-mediated autophagy (CMA) and both processes do not require autophagosome formation. Invagination of the lysosome/vacuole membrane during micro-autophagy directly engulfs small cytosolic components (Sahu et al., 2011). In contrast, in CMA, cytosolic proteins containing a KFERQ motif are recognized by the chaperone protein heat shock cognate 70 (HSC70; also known as HSPA8) and directly translocate across the lysosomal membrane (Orenstein and Cuervo, 2010). In response to starvation, autophagy is mainly considered a bulk process that unselectively degrades cellular material to meet the energy needs of cells (Tooze and Yoshimori, 2010). However, autophagy can also selectively target distinct organelles and cellular structures that are damaged and/or need to be turned over (Rogov et al., 2014). Although ER membranes had been observed inside lysosomes after phenobarbital treatment (Bolender and Weibel, 1973) or in autophagosomes in yeast (Hamasaki et al., 2005), the ER was initially primarily considered as the major source of autophagosome membranes (Hayashi-Nishino et al., 2009; Ylä-Anttila et al., 2009), and ER membranes inside the autophagosomes were seen as an effect of the general autophagy process due to bulk engulfment of the cytosol. Only in the past few years, has the specific elimination of the ER been classified as a selective form of autophagy (denoted ER-phagy) and specific receptors have been characterized.

Various organelles have been shown to provide membrane for autophagosome formation (Bodemann et al., 2011; Hailey et al., 2010; Ravikumar et al., 2010); nevertheless, the major source of autophagic membrane, which subsequently forms autophagosomes, is the ER (Lamb et al., 2013). Autophagic membrane can be generated from the entire ER body, as well as from the contact sites between ER and mitochondria (mitochondria-associated membranes; MAMs) or between ER and plasma membrane (Hamasaki et al., 2013; Nascimbeni et al., 2017). Moreover, the ER is the natural harbor of many proteins of the autophagy machinery. Autophagic membranes originate from ER structures called omegasomes, which are enriched in the phospholipid phosphatidylinositol 3-phosphate [PI(3)P] as well as the PI(3)P-binding protein DFCP1 (also known as ZFYVE1) (Axe et al., 2008) (see poster). Controlled assembly of the phosphoinositide 3-kinase (PI3K) complex is therefore critical for autophagosome formation, as PI(3)P recruits and anchors several downstream factors of the autophagy machinery (Matsunaga et al., 2010; Molejon et al., 2013; Polson et al., 2010). Moreover, the LC3 conjugation machinery (see below) recruits and conjugates the members of the ubiquitin-like protein family to autophagic membrane (Kabeya et al., 2004). A general introduction into selective autophagy, as well as a detailed description of individual selective ER-phagy pathways, will be provided below and on the poster. Many more selective autophagy pathways exist, including those essential for the maintenance and turnover of other cellular organelles than the ER, but these will not be further addressed in this article.

Selective autophagy pathways

Selective autophagy facilitates the targeted elimination of specific organelles or cargos through the action of specific autophagy receptors, which recruit and sequester cargo into autophagosomes (Stolz et al., 2014). Autophagy receptors often belong to a specific organelle proteome and their characteristic feature is the ability to directly bind to the LC3/GABARAP family members [LC3A, LC3B, LC3C (also known as MAP1LC3A, MAP1LC3B and MAP1LC3A, respectively), GABARAP, GABARAP-L1 and GABARAP-L2; Atg8 in yeast] through a LC3-interacting region (LIR; AIM for Atg8-interacting motif in yeast), as well as the autophagic cargo (Rogov et al., 2014, 2017). Because of their interaction with the ATG8 family, classical autophagy receptors are continuously degraded in the lysosome resulting in low basal levels. Genetic inactivation of specific autophagy receptors abolishes the removal of the target organelle, but it does not affect other forms of selective autophagy or unspecific macro-autophagy (Rogov et al., 2014; Stolz et al., 2014). Autophagy receptors may also accomplish other biological functions not necessarily related to autophagy. Some examples are the mitophagy receptors prohibitin 2 (PHB2) and FUNDC1 (Liu et al., 2012; Wei et al., 2017). PHB2 is an inner mitochondria membrane protein involved in the control of the functional integrity of the organelle (Merkwirth and Langer, 2009), while FUNDC1 maintains ER–mitochondria interactions (Muñoz and Zorzano, 2017). Below, we will discuss the pathways of ER-phagy that have been so far described in yeast and mammals.

ER-phagy in yeast

In yeast, the ER provides membranes for autophagosomes and, at the same time, is itself a target of autophagy. The term ER-phagy was used for the first time by Peter Walter's group in describing how, within the unfolded protein response (UPR), ER whorls become selectively degraded by the vacuole (Bernales et al., 2006; Schuck et al., 2009). During UPR conditions, the ER significantly enlarges its volume and membrane content. However, soon after, cells start to re-establish the initial ER homeostasis by eliminating superfluous membrane via vacuolar degradation (Schuck et al., 2014). This can also function as a detoxification system in which aggregated or otherwise unwanted proteins are constricted to defined ER compartments and subsequently eliminated by the vacuole (Cebollero et al., 2012; Yorimitsu and Klionsky, 2007). The initial hypothesis was that the utilized autophagy pathway may differ depending on the initial stress and on the affected organism (Bernales et al., 2006; Ogata et al., 2006; Yorimitsu et al., 2006). Initially, the ER whorls formed upon treatment with DTT and tunicamycin were thought to be degraded through autophagosomes. However, later studies from the same laboratory showed the dispensability of the typical core autophagy machinery, with the cargo being directly absorbed by the vacuole via the micro-autophagy pathway (Schuck et al., 2014). More recently, it has been shown that ER fragments can also be sequestered into Atg8-positive autophagosomes upon nutrient starvation or TOR inhibition by rapamycin (Mochida et al., 2015). This pathway required the ER-phagy receptors Atg39 and Atg40, two ER membrane proteins that bind Atg8 through an AIM (see poster). Interestingly, Atg39 and Atg40 are not homologous to each other and are present in two distinct ER subdomains; Atg39 is a transmembrane protein

Journal of Cell Science (2018) 131, jcs217364. doi:10.1242/jcs.217364

specifically located to the perinuclear ER, while Atg40 is an intramembrane protein mainly found in the cortical ER. In accordance with their subcellular location, perinuclear ER degradation is affected mostly by the absence of Atg39, whereas *ATG40* ablation has major effects on cortical ER degradation (Mochida et al., 2015). However, it remains to be investigated whether these two receptors also co-operate within common ER-phagy pathways. Of note, lack of Atg39 and Atg40 does not influence the general macro-autophagy flux or other selective autophagy pathways, such as mitophagy and pexophagy (Mochida et al., 2015).

ER-phagy in mammalian cells

In mammalian cells, degradation of ER components by autophagy was discovered as a back-up system for the inefficient proteasomal degradation of ER proteins through the ER-associated protein degradation (ERAD) pathway (Fujita et al., 2007; Hidvegi et al., 2010; Houck et al., 2014; Ishida et al., 2009). In addition, autophagy may control ER shape and function in T and B lymphocytes (Jia et al., 2011; Pengo et al., 2013). Even though the process was termed reticulophagy at the time, from a current view, the basal turnover and re-shaping after ER expansion upon stress, as well as the lysosomal degradation of protein aggregates within the ER lumen, are all specific branches of ER-phagy. Specialized ER-phagy receptors operating to regulate individual aspects have been identified in the past few years, with FAM134B (also known as RETREG1) being the first one to be described and characterized (Khaminets et al., 2015) (see poster).

Ablation of *FAM134B* or inactivation of the LIR domain have been shown to block ER fragmentation and subsequent lysosomal degradation under both basal conditions and starvation. Initially, FAM134B was described as a Golgi protein responsible for the pathogenesis of a sensory and autonomic neuropathy (HSAN-II) (Kurth et al., 2009). Since then, FAM134B has also been classified as an intra-membrane ER-resident protein that is characterized by the presence of a reticulon homology domain (RHD) and that is mainly located at the edges of the ER sheets. FAM134B has the intrinsic property to bend double layer ER membranes and, *in vitro*, to reduce the size of liposomes (Khaminets et al., 2015). The precise molecular mechanism underlying the ER sheet fragmentation is still unclear, but recent findings indicate that atlastin 2 (ATL2), a GTPase-mediating homotypic fusion of the ER, is an essential component of FAM134B-mediated ER fragmentation (Liang et al., 2018preprint). The discovery of FAM134B was followed by the characterization of additional ER-phagy receptors: SEC62, RTN3 and CCPG1 (Fumagalli et al., 2016; Grumati et al., 2017; Smith et al., 2018) (see poster).

RTN3 is a RHD-containing protein that is located at ER tubules and involved in their specific turnover following starvation (Grumati et al., 2017). As a member of the reticulon family, RTN3 has been previously implicated in the formation of ER tubules (Voeltz et al., 2006). However, RTN3 has multiple splicing isoforms and only the longest isoform of RTN3 carries six active LIR domains in its extended N-terminal domain, which are essential for LC3/GABARAP binding, fragmentation of ER tubules and its function as an ER-phagy receptor (Grumati et al., 2017). The oligomerization of the long RTN3 isoforms appears to be critical for the initiation of ER-phagy foci (Grumati et al., 2017), as the local concentration of RTN3 LIR domains enables the recruitment and clustering of a large amount of LC3 proteins and acts as a wedge to constrict the ER tubules, thereby favoring their breakage. Of note, RTN3 and FAM134B do not directly interact with each other and – similar to Atg39 and Atg40 in yeast – their primary function as ER-phagy receptors is restricted to the respective ER subdomain they reside in (Grumati et al., 2017) (see poster).

In addition, specialized ER-phagy receptors have been identified that respond to an overload of the ER with misfolded or aggregated proteins. CCPG1 is one of them, and its expression is upregulated in response of UPR induction. CCPG1 comprises an N-terminus carrying a single LIR motif and two FIP200-interacting regions (FIRs) devoted to the interaction with FIP200 (also known as RB1CC1), a transmembrane domain and an ER-luminal C-terminus. Even though the molecular mechanism has still not been completely elucidated, the C-terminal domain potentially can recognize and bind to misfolded or aggregated cargo within the ER lumen, while the cytosolic LIR and FIR domains promote the local clustering of CCPG1–cargo complexes and recruit autophagic membrane. *In vivo*, CCPG1-mediated ER-phagy protects pancreatic acinar cells against the aggregation of ER luminal proteins. Therefore, CCPG1 may act as a bridge between UPR signaling and ER-phagy in a physiological context (Smith et al., 2018).

During UPR, mammalian cells expand their ER to counteract stress. However, in contrast to what is seen in yeast, mammalian cells do not appear to use micro-autophagy to re-establish ER shape and homeostasis. Instead, once the stress stimulus is resolved, the translocon component SEC62 acquires a new biological function and becomes an ER-phagy receptor to mediate the so-called recovER-phagy through a LIR motif in its C-terminal cytosolic domain (Fumagalli et al., 2016) (see poster). This particular form of ER-phagy aims to eliminate excessive ER membranes that have been generated during the acute UPR phase. It is thought that SEC62 exits the translocon complex before acting in ER-phagy, which is therefore functionally separated from protein translocation. In line with this notion, functional disturbance of the translocon complex upon the genetic inactivation of the translocon component *SEC63* does not affect the role of SEC62 in selective autophagy (Fumagalli et al., 2016).

Taken together, mammalian cells have developed a variety of ER-phagy receptors, which are active under specific conditions to handle the respective stress situations. Similar to Atg39 and Atg40 in yeast, the ablation of FAM134B and RTN3 also does not affect the general macro-autophagy flux and, in the case of FAM134B, the selective elimination of proteins aggregates (aggrephagy) is also not compromised (Grumati et al., 2017; Khaminets et al., 2015). A possible regulative role of SEC62 and CCPG1 in the macro-autophagy process or any other form of selective autophagy has not been investigated to date. However, from the cellular phenotype that has been described in their absence, it appears at the moment rather unlikely that they have a relevant role in autophagic pathways other than ER-phagy.

ER-phagy in human diseases

Defects in autophagy pathways are associated with multiple human pathologies, including infectious and neurodegenerative diseases, aging and cancer (Dikic and Elazar, 2018). In case of deficient ER-phagy, the impact on infectious disease is particularly evident: the ER is often exploited by viruses and bacteria during their infection cycles; for instance, Dengue, Zika, West Nile and Ebola viruses all assemble and mature in and at the ER (Junjhon et al., 2014; Welsch et al., 2009). In fact, ER-phagy is thought to be an active defense mechanism of the host cell to eliminate viruses or bacteria contained in ER compartments. While the molecular mechanisms are not yet fully understood, it is already known that FAM134B and RTN3 can restrict replication of different viruses

Journal of Cell Science (2018) 131, jcs217364. doi:10.1242/jcs.217364

(Chiramel et al., 2016; Lennemann and Coyne, 2017; Wu et al., 2014). Nevertheless, viruses co-evolved and learned how to escape ER-phagy. Indeed, the hepatitis C virus (HCV) protease NS3 cleaves FAM134B within its RHD, thereby destroying the structure of the RHD domain. The direct consequence is the impairment of the ability of FAM134B to bend the ER membrane and promote ER-phagy (Lennemann and Coyne, 2017). Flavivirus NS3A protein directly interacts with RTN3 in order to remodel ER membranes and so generates their own vesicle packets (Aktepe et al., 2017). Moreover, in phagocytes, ER-phagy is considered a stress-induced response mechanism to intracellular live Gram-positive bacteria that alleviates ER stress and promotes phagocyte survival after infection (Moretti et al., 2017). However, the underlying molecular mechanisms are still not clear and it is not known if and how ER-phagy receptors are potentially involved.

The impact of ER-phagy on neuronal homeostasis and neurodegenerative diseases is less clear. Even though FAM134B has been directly linked to the pathogenesis of hereditary sensory neuropathy HSAN-II (Kurth et al., 2009; Murphy et al., 2012), the molecular mechanism through which FAM134B causes the pathology is only partially understood. The ER interfuses neurons from the cell body to the very tip of the axons, and impairment of FAM134B-mediated basal ER turnover leads to progressive ER stress and affects the survival of sensory and autonomic neurons (Khaminets et al., 2015). RTN3 has also been reported to be involved in the etiology of neurodegenerative diseases, more specifically in Alzheimer's disease (Shi et al., 2009; Small and Gandy, 2006). However, the respective experimental analyses mostly concentrated on the short rather than the long isoforms (carrying the LIR motifs) of RTN3, so the potential impact of ER-phagy remains elusive.

Furthermore, a role of ER-phagy – via FAM134B and SEC62 – in cancer development and progression has also been reported. For example, mutations in FAM134B have indicated a dual role in carcinogenesis. In esophageal squamous cell carcinoma, FAM134B acts as an oncogene and promotes cancer development. By contrast, it has a tumor-suppressive function in colon and breast cancer that is well established (Islam et al., 2017; Tang et al., 2007). SEC62 is also amplified in several cancers with a yet undefined molecular role (Hagerstrand et al., 2013; Wemmert et al., 2016). Because a well-established function of SEC62 is to resolve ER stress, it is important to emphasize that the UPR has a dual impact on tumors: it can support cancer cell growth, providing a machinery to deal with stress, but, on the other hand, it can have a cytotoxic effect and induce cell death via apoptosis. The molecular basis for the involvement of FAM134B in cancer might arise along the same lines. A misbalance of ER content caused by FAM134B impairment may trigger stress responses or prolonged and/or disturbed signaling of cascades that are triggered by ER-localized membrane proteins.

Finally, the biological function of CCGP1 is only emerging; however, its relevance for ER homeostasis in pancreatic cells already hints to a potential impact on pancreatic disorders (Smith et al., 2018).

Overall, ER-phagy receptors are involved in a complex network of cellular signaling pathways and, therefore, have a role in a multitude of human diseases. Hence, it is imperative to investigate their molecular mechanisms in order to find a developmental impetus for therapeutic approaches.

Conclusions and future perspectives

ER-phagy is the most recently identified form of selective autophagy and there are still many open questions regarding its physiological role, regulation and molecular mechanisms. Apart from CCPG1, ER-phagy receptors do not possess a notable ER-luminal domain; it is therefore likely that an apparatus of co-factors coordinates the crosstalk between the ER-luminal cargo and receptors that only have intramembrane domains, such as FAM134B and RTN3. At the same time, specific ER-luminal proteins might sense cargo, thereby promoting its local restriction and/or the binding to ER-phagy receptors for subsequent sequestration into ER-derived autophagic vesicles.

With respect to signaling, the causes of stress and type of tissue involved may determine the final autophagic response and activate different signaling cascades. Almost certainly, ER-phagy receptors undergo some post-translational modifications that initiate structural changes, binding of co-factors or oligomerization. Of note, amino acid sequences flanking the LIR domains of ER-phagy receptors do contain serine and threonine residues that could be phosphorylated, leading to increased affinity for LC3 proteins (Wild et al., 2011).

As described above, individual ER-phagy receptors are specialized with regard to the ER subdomains or stress responses and, moreover, their expression levels differ in individual tissues. Specialized cells are characterized by a certain ER morphology and function. The ER in the secretory cells mainly consists of sheets, whereas in neurons, tubules are the main substructure. For this reason, specific types of cells might uniquely express specific ER-phagy receptors, which, at the same time, might not compensate for each other. However, it is not clear yet how the functions of the receptors are related to each other. FAM134B and RTN3 act separately and this is likely owing to their distinct spatial distribution. Nevertheless, functional interactions among some receptors are plausible under particular circumstances during the ER-phagy process. It is conceivable that the reticulon-type receptors FAM134B and RTN3 act as receptors for the basal ER turnover due to their ability to remodel, bend and fragment ER sheets and tubules. Through a different process, the transmembrane receptors Sec62 and CCPG1, which are not intrinsically able to modify the ER network, may act as cargo-detecting receptors, which instead link damaged ER portions to the autophagy machinery and favor the separation and delivery of ER-containing autophagic vesicles.

Currently, it is still difficult to quantify to what extent ER-phagy contributes to ER homeostasis as it cannot only remodel different ER subdomains but also could rebalance the entire ER network to accomplish physiological functions or to resolve harmful stress situations. Considering the substantial findings in the past few years and the large amount of remaining open questions, future studies will hold exciting insights into ER biology.

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Competing interests

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A high-resolution version of the poster and individual poster panels are available for downloading at http://jcs.biologists.org/lookup/doi/10.1242/jcs.217364.supplemental

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