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REVIEW

# Stay in touch with the endoplasmic reticulum

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**The endoplasmic reticulum (ER), which is composed of a continuous network of tubules and sheets, forms the most widely distributed membrane system in eukaryotic cells. As a result, it engages a variety of organelles by establishing membrane contact sites (MCSs). These contacts regulate organelle positioning and remodeling, including fusion and fission, facilitate precise lipid exchange, and couple vital signaling events. Here, we systematically review recent advances and converging themes on ER-involved organellar contact. The molecular basis, cellular influence, and potential physiological functions for ER/nuclear envelope contacts with mitochondria, Golgi, endosomes, lysosomes, lipid droplets, autophagosomes, and plasma membrane are summarized.**

**endoplasmic reticulum | nuclear envelope | mitochondria | Golgi apparatus | endosome | lysosome | lipid droplets | autophagosome | plasma membrane | membrane contact site**

## Introduction

Membrane-bound organelles in eukaryotic cells compartmentalize cellular components, allowing distinct biochemical reactions to proceed independently within confined spaces. This compartmentalization largely enhances the efficiency and accuracy of cellular metabolism. However, it inevitably creates obstacles for signal transduction and material exchange between the organelles. To avoid such issues, organelles often physically interact with each other via a membrane contact site (MCS) formed by a combination of membrane proteins and/or lipids from both sides (Cohen et al., 2018; Helle et al., 2013; Simoes et al., 2020).

MCSs generally form between two functionally synergistic organelles in cells, with protein composition characterizing the microdomains of the MCSs for the formation of a tight association between the organelles. Although membranes from both organelles are in close contact at the MCS, these membranes do not fuse and maintain their distinct identities. The structure of the MCS is relatively stable and can be revealed by electron microscopy and fluorescence microscopy, suggesting that these maintained contacts between the organelles have significant functions (Csordas et al., 2018). Studies on the structures, components, and functions of MCSs have significantly increased in the last decade. It is now clear that different MCSs may exist in the same set of organelles and perform distinct functions. Various MCSs may have a much broader range of biological roles in cells.

Among intracellular structures, the endoplasmic reticulum (ER) is a complicated network with abundant membrane surface (Baumann and Walz, 2001). Within the ER, different morphological regions, including tubules and sheets, make contact with a variety of organelles for different purposes (Zhang and Hu, 2016). As the starting point of the endomembrane system, the ER naturally communicates with other endomembrane organelles, including Golgi, endosomes, lysosomes, assorted vesicles, and the plasma membrane (PM), not only through vesicular trafficking, but also by establishing MCSs. In addition, the ER stays in touch with mitochondria, autophagosomes, and lipid droplets (LDs), and other organelles. These contacts have a profound impact on the dynamics and functions of the ER and its surrounding intracellular compartments.

## ER-mitochondria contact

Mitochondria play a central role in cellular metabolism; it is the site of ATP synthesis through oxidative phosphorylation, the TCA cycle, and iron-sulfur cluster biogenesis, among other processes. Recent studies indicate that inter-organelle contacts extensively regulate mitochondrial function. Among these contacts, ER-mitochondria (ER-mito) contact sites are relatively stable and important for lipid transport, mitochondria dynamics, $Ca^{2+}$ homeostasis, reactive oxygen species (ROS) signaling, autophagy, organelle trafficking/positioning, and internal orga-

nization of the mitochondria. ER-mito contact dysfunction causes numerous diseases, including neurodegenerative diseases, diabetes, and cancer.

## Lipid transport

Compared with vesicular lipid transport, the non-vesicular lipid transport mediated by hydrophobic grooves or small pockets containing lipid transport proteins (LTPs) is a more efficient and direct route. A number of LTPs localize at the ER-mito MCSs. In yeast, the ER and mitochondria are tethered by the ER-mito encounter structure (ERMES) complex (Kopec et al., 2010). This complex has four subunits, three of which (Mmm1, Mdm12, and Mdm34) have synaptotagmin-like mitochondrial-lipid-binding (SMP) domains (Kopec et al., 2010), which is a characteristic of MCS-based LTPs in both yeast and mammals (Kopec et al., 2010; Schauder et al., 2014), indicating a role in lipid transfer.

Yeast cells with ERMES deletions are viable despite growth defects (Lang et al., 2015), suggesting that there are other redundant pathways for ER-mito lipid exchange. Yeast VPS13, which is involved in vacuolar protein sorting (VPS), was identified as an LTP that bypasses ERMES function (Park and Neiman, 2012; Park et al., 2016). It localizes to ER-vacuole contact sites, in addition to ER-mito contact sites, and the double deletion of VPS13 and ERMES causes lethality (Bean et al., 2018; Kumar et al., 2018; Li et al., 2020; Park and Neiman, 2012; Park et al., 2016; Yeshaw et al., 2019). Although the EMERS counterpart in high eukaryotes is yet to be identified, VPS13 is conserved throughout eukaryotic cells. Follow-up research has shown that the large (>3,000 amino acids) VPS13 has a very long hydrophobic groove (Kumar et al., 2018; Li et al., 2020), supporting its function in lipid transport. There are four human VPS13 proteins, among which, VPS13A localizes at both the ER-mito MCSs and ER-LD contacts (Kumar et al., 2018). The FFAT motif in the middle of VPS13A interacts with an ER membrane protein, vesicle-associated membrane protein associated protein A (VAP-A) (Kumar et al., 2018; Loewen et al., 2003), linking the ER to mitochondria. However, how VPS13A engages mitochondria remains elusive. VPS13A has been shown to transfer several phospholipids, including phosphatidic acid (PA), which supports the synthesis of cardiolipin (CL), a key component of the inner mitochondrial membrane (IMM) (Kameoka et al., 2018). A rare, Huntington-like neurodegenerative disease, Chorea acanthocytosis, has been reported to be caused by a conserved region mutation in VPS13s (Kumar et al., 2018; Rampoldi et al., 2001; Ueno et al., 2001). Considering the localization of VPS13A, the membrane growth defect and alteration of mitochondrial lipid composition may play roles in its disease pathogenesis. In addition, VPS13C at ER-lysosome contact sites (Kumar et al., 2018) may perturb lipid homeostasis and indirectly disturb mitochondrial metabolism (Kumar et al., 2018; Munoz-Braceras et al., 2019).

ER-localized VAP-B also interacts with several LTPs at ER-mito contact sites; binding partners include the mitochondrial protein PTPIP51, which regulates calcium homeostasis (De Vos et al., 2012). The complex has been proposed to facilitate PA transfer between the two organelles, supporting the synthesis of CL (Stoica et al., 2014). Recently, mitoguardin-2, a mitochondrial protein involved in both ER-LD and ER-mito contact sites has been identified as yet another LTP (Hong et al., 2022) (Figure 1). The preference for these LTPs at ER-mito contact sites is yet to be determined. Other questions, such as why so many transporters are needed, how they orchestrate the transfer of lipids, and whether redundancy is involved in regulatory roles, remain unanswered.

## Mitochondrial fission and fusion

Mitochondria dynamics, including fission and fusion, are closely coupled with their functions and regulated by ER-mito contact

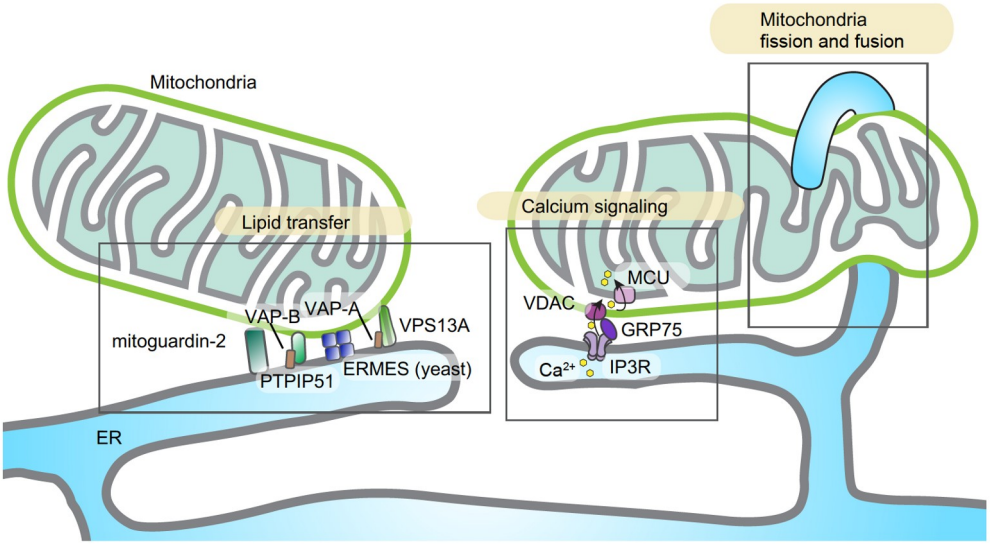



**Figure 1.** ER-mitochondria contact sites and their functions. ER-mito contact sites are involved in the regulation of lipid transport, mitochondria dynamics, $Ca^{2+}$ homeostasis, ROS signaling, autophagy, and organelle trafficking/positioning, among other functions. Lipid transfer processes at the ER-mito contact sites are mediated by VAP, its partners VPS13A and PTPIP51, and mitoguardin-2, as well as ERMES in yeast. ER-mito MCSs play a primary role in the regulation of cellular $Ca^{2+}$ channeling through the VDAC/IP3R/GRP75 complex. The inner mitochondrial membrane-localized mitochondrial calcium uniporter protein (MCU) allows $Ca^{2+}$ entry into the mitochondrial matrix and is closely linked with the VDAC/IP3R/GRP75 complex. ER tubules wrap around mitochondria, defining the constriction sites for fission. Mitochondrial fusion is also related to the ER-mito contact sites as described in the text.

(Friedman et al., 2011). ER tubules wrap around mitochondria in coordination with actin polymerization (Korobova et al., 2013; Manor et al., 2015) to define the constriction sites upstream of DRP1, the large dynamin-related GTPase known to be responsible for mitochondria fission (Smirnova et al., 1998). In yeast, Miro GTPase Gem1, together with ERMES, is involved in the ER wrapping interaction with mitochondria and regulates the mitochondrial DNA distribution (Murley et al., 2013). Recent studies distinguish the differences between "midzone" and "peripheral" mitochondrial fission, which are associated with mitochondrial proliferation and mitophagy, respectively. Distinct fission signatures predict mitochondrial degradation or biogenesis (Kleele et al., 2021). Furthermore, the midzone fission sites consistently contact the ER before fission, but most peripheral fission sites do not (Kleele et al., 2021).

Similarly, mitochondrial fusion events are tightly linked to ER-mito contact (Guo et al., 2018). Because lipid transfer occurs frequently at the contact site and lipid species are key players in fusion reactions, contact-linked mitochondrial fusion is likely related to lipid homeostasis. Loss of VAP-A disrupts the mitochondrial morphology and fusion capacity, likely because IMM fusion depends on the CL composition (Ban et al., 2017; Faelber et al., 2019), which is sensitive to contacts formed with the ER (Figure 1). Consistently, the modified outer mitochondrial membrane (OMM) carrier MTCH2 promotes mitochondrial fusion by regulating lipogenesis (Labbe et al., 2021), even though the same carrier was proposed to also serve as a protein insertase on mitochondria (Guna et al., 2022). OMM fusogen mitofusin 2 (MFN2) has been proposed to tether the ER to mitochondria (de Brito and Scorrano, 2008), though homotypic tethering requires the presence of MFN2 on the ER (de Brito and Scorrano, 2008), which is highly debatable and less likely (Filadi et al., 2015). Nevertheless, it is conceivable that MFN is enriched in the ER contact sites.

## Cell signaling

ER-mito contact sites play an important role in the regulation of cellular $Ca^{2+}$ channeling between the two organelles. Mitochondrial $Ca^{2+}$ levels control many aspects of the known mitochondrial functions, including signaling, oxidative metabolism, ROS generation, and cell death. The local uptake of $Ca^{2+}$ possibly increases TCA cycle metabolism and promotes electron transport complex activity (Nemani et al., 2020), and the ER simply serves as the major reservoir for cellular $Ca^{2+}$. $Ca^{2+}$ exchange at ER-mito contact sites is mediated by a complex made up of the mitochondria-localized protein voltage-dependent anion-selective channel (VDAC), the mitochondria-localized heat shock protein chaperone GRP75, and the ER-localized inositol 1,4,5-trisphosphate receptors (IP3Rs) (Rizzuto et al., 1993; Szabadkai et al., 2006). Moreover, the mitochondrial calcium uniporter protein (MCU) (Baughman et al., 2011; Qi et al., 2015) localized at the IMM allows $Ca^{2+}$ entry into the mitochondrial matrix and is closely linked to the VDAC/IP3R/GRP75 complex (Baughman et al., 2011; Hayashi et al., 2009; Pallafacchina et al., 2021) (Figure 1). Recently, DJ-1, encoded by *PARK7*, one of the genes associated with early-onset familial forms of Parkinson's disease (PD), was reported to be the additional unit of the VDAC/IP3R/GRP75 tether in muscle cells, also playing roles in $Ca^{2+}$ channeling at the ER-mito contact sites (Liu et al., 2019b). $Ca^{2+}$ channeling defects promote apoptosis and are linked to diseases (Orrenius et al., 2003). IP3R1 mutation has been reported to be linked to type 2 diabetes/obesity (Arruda et al., 2014). In stress conditions, the ER chaperones elevate $Ca^{2+}$ signaling at the ER-mito contact sites, further stimulating oxidative phosphorylation in mitochondria or apoptosis (Gutierrez and Simmen, 2018).

Both mitochondria and the ER serve as critical intracellular redox hubs, facilitating $Ca^{2+}$-dependent generation of redox nano-domains at ER-mito contact sites. These nanodomains are formed by $H_2O_2$ release in conjunction with $Ca^{2+}$ release, leading to $K^+$ and water influx into the mitochondrial matrix. Consequently, the mitochondrial cristae volume is reduced, resulting in the release of $H_2O_2$. Importantly, the trans-organellar transport and diffusion of ROS appears to be a tightly regulated process, but the detailed mechanism is largely unknown.

Redox-sensitive proteins, such as TMX1, ERO1a, and SERCA, have been reported to be enriched in the ER-mito contact sites, where they play a vital role in reducing the level of ROS and are themselves regulated by ROS (Yoboue et al., 2018; Zhang et al., 2019). In addition, ROS signaling has been observed in the ER, mitochondria, and peroxisome, with these three organelles forming the intriguing "redox triangle" (Wanders et al., 2016), an entity that is evidently contact-dependent.

## Autophagy

Autophagy occurs under conditions of nutrient stress, and the ER-mito contact sites have been reported to play roles in this process (Hamasaki et al., 2013). In yeast, the ERMES complex is dispensable for the nonselective bulk autophagy (Bockler and Westermann, 2014). In mammalian cells, when starvation-induced autophagy occurs, the ER protein BECN1 and Parkin (Gelmetti et al., 2017), which are key components in formation of the autophagosome, will move to the ER-mito contact sites or mitochondria-associated membranes (MAMs) to initiate the formation of an omegasome for further mitophagy.

ERMES-mediated contact couples mitophagy with mitochondrial fission. For mitophagy, the mitochondria need to be separated first, and then are engulfed by the omegasome; the separation process is closely linked to the fission involving the ER-mito contact sites (Kleele et al., 2021). ER-mito contact also regulates autophagy through the $Ca^{2+}$ level, as the $Ca^{2+}$ levels in mitochondria trigger the activation of autophagy-related proteins (Gomez-Suaga et al., 2017).

Pexophagy, the degradation of peroxisomes by autophagy, has been shown to be linked to ER-mito contact. Pex11, a peroxisomal membrane protein, interacts with ERMES, and the pexophagy process is dependent on the interaction (Mattiazzi Ušaj et al., 2015).

## Nuclear envelope-mitochondria contacts

The nuclear envelope (NE) is regarded as a special ER because the outer nuclear membrane (ONM) is an extension of the ER, faces the cytoplasm like other ER, and possesses similar morphology and composition as the ER (Güttinger et al., 2009). However, the inner nuclear membrane (INM) of the NE directly faces the nucleoplasm and possesses specific components different from the regular ER (Ungricht and Kutay, 2017). The NE may directly synergize simultaneously with the nucleoplasmic compartments, cytoplasmic cytosol, and membranous organelles, allowing the


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mitochondria to contact the NE and ER to form NE-mitochondria MCSs and ER-mito MCSs.

Using a high-throughput screen in *Saccharomyces cerevisiae*, Eisenberg-Bord et al. (2021) found that the NE protein contact nucleus mitochondria 1 (Cnm1) and OMM protein Tom70 co-regulate the formation of NE-mitochondria MCSs independent of ER-mito MCSs. Cho2, Opi3, and Ino2 regulate Cnm1 abundance through their effect on phosphatidylcholine (PC) levels. Lower levels of PC may lead to a decrease in Cnm1-mediated NE-mitochondria MCSs, which can be rescued by supplying choline (Eisenberg-Bord et al., 2021).

The NE-mitochondria MCSs in yeast cells are generally stable, but this is not the case in mammalian cells. The mechanism triggering non-persistent NE-mitochondria MCS formation is unclear. In mammalian cells, interactions between the mitochondria and nucleus are usually accompanied by some functional responses under special conditions. For example, the formation of contact sites between the mitochondria and nucleus benefits communication between the two organelles during the mitochondrial retrograde response (MRR) and proliferative stimuli. The translocator protein-mediated protein complex TSPO-ACDB3-PKA-AKAP95 tethers the mitochondria to the nucleus during MRR, promotes nuclear stabilization of prosurvival transcription factors, such as NF-κB, and regulates cholesterol transport between the nucleoplasm and cytoplasm (Desai et al., 2020). This contact may represent a defensive mechanism in response to apoptotic cues in the short term, and cholesterol may serve as a second messenger for mitochondria-nucleus retrocommunication in the presence of ROS and $Ca^{2+}$ signaling (Desai et al., 2020). In *Plasmodium falciparum*-infected cells, proximity and interaction between the mitochondrion and nucleus may contribute to cell survival via the MRR (Connelly et al., 2021). Upon exposure to proliferative stimuli, such as serum, epidermal growth factor (EGF), and hypoxia, the mitochondria may cluster around the nucleus and tether onto the NE via MFN2-enriched NE-mitochondria MCSs (Zervopoulos et al., 2022). Through the MFN2-mediated contacts, mitochondrial pyruvate dehydrogenase complex (PDC) is deposited onto the NE and then released into the nucleus without the involvement of nuclear pore complexes (Zervopoulos et al., 2022). Some research has shown that NE-mitochondria MCSs also contribute to the development of cancer by changing metabolic pathways (Kinnaird et al., 2016).

As there is a close and special relationship between the NE and ER, it is difficult to distinguish the contact of an organelle with either the NE or ER. Although most functions of the NE-mitochondria MCSs are thought to be the same as those of the ER-mito MCSs, the specific functions of the NE-mitochondria MCSs, especially in mitosis, are worth in-depth studies.

## Contacts in mitosis

Although a variety of ER-mito contacts have been identified during interphase (Gómez-Suaga et al., 2018), those in mitosis remain limited. During mitosis, the dramatic morphological change in the NE and ER, as well as the incorporation of NE components into the ER, make the mitotic ER unique (Carlton et al., 2020; Champion et al., 2017). Through this incorporation, the nuclear membrane components may provide a new cytosolic side-facing scaffold in the mitotic ER and increase the opportunities for the mitotic ER to contact various other organelles. In addition, the classical INM protein emerin has been identified in MAMs and may be a tether protein that links the mitochondria and nucleus (Doghman-Bouguerra et al., 2016). Cellular activities in mitosis also require an expanded energy supply, and the mitochondria may uptake more $Ca^{2+}$ for generation of the expanded energy (Zhao et al., 2019). This suggests that either the functions of the regular ER-mito contact sites in mitosis are up-regulated, or that mitosis-specific ER-mito contact sites exist to regulate $Ca^{2+}$ flow from the ER to the mitochondria. Therefore, there are still much to learn about how functional coordination occurs between the mitotic ER and mitochondria through MCSs.

## New tools

Along with the growing focus on ER-mito contact sites, new tools for qualitative and quantitative analysis are emerging, including various advanced techniques, such as proximity biotinylation, cutting-edge methods of mass spectrometry, the evolution of super-resolution microscopes, cryo-electron microscopy (cryo-EM), correlative light and electron microscopy (CLEM), and the widespread application of deep learning-based approaches. Several of these cutting-edge tools have significantly contributed to decoding the protein and lipid compositions at the ER-mito interface. For example, endogenous proteins on the OMM and ER membrane of living human fibroblasts were successfully identified using peroxidase-mediated proximity biotinylating. Dataset intersection identified protein candidates localized to ER-mito contact sites, demonstrating the potential of proximity biotinylation for uncovering the molecular composition and functions of MCSs (Hung et al., 2017).

Peroxidase-mediated proximity biotinylating has since been improved and modified. A new approach called Contact-ID, using a split-pair system of BioIDs, successfully identified new MAM-specific proteins in live cells (Kwak et al., 2020). These proteins were mainly annotated with OMM and ER membrane functions related to MAMs. Contact-ID also revealed the membrane topologies of the integral membrane proteins and identified regulatory proteins for MAM formation, making it a valuable tool for profiling organelle-MCSs in live cells.

To determine the lipid types transported between organelles, *in vivo* radiolabeled precursor determination and *in vitro* lipid exchange assays are commonly used. Recently, a versatile method named METALIC (Mass tagging-Enabled TrAcking of Lipids In Cells) was developed to track inter-organelle lipid flux inside cells (John Peter et al., 2022). The strategy exploits enzyme CFAse-mediated mass tagging to measure the exchange of specific lipids between organelles *in vivo*. Using this approach, the *in vivo* lipid transport activity of VPS13 and ERMES was quantified.

One example of the deep-learning for contact site research is "DeepContact", which is a deep-learning protocol for optimizing organelle segmentation, particularly the ER and mitochondria, and contact analysis based on label-free electron microscopy (Liu et al., 2022). Using DeepContact, researchers unveiled the rearrangements of different types of MCSs in different nutritional conditions, including the change in ER-mito and LD-mitochondria contact (Liu et al., 2022). Another breakthrough is that DeepContact does well in the quantitative analysis of MCSs in tissues, which are tightly related to pathological and physiological processes (Liu et al., 2022). Using DeepContact to analyze the tissue model, researchers found that Sertoli cells, which provide structural support and nourishment for spermatogenesis,

exhibit different ER-mito contact profiles in different stages of the epithelium, accompanied by morphological shifts in these organelles (Liu et al., 2022). Importantly, the changes in ER-mito contact correlate with the stage transition during spermatogenesis, indicating that the MCS states are tightly associated with the functional switching (Liu et al., 2022). DeepContact allows the detection of parameter shifts for the ER and mitochondria and ensures high throughput analysis of even subtle alterations in contact profiles (Liu et al., 2022).

## ER-Golgi contact

The ER-Golgi system consists of the ER, Golgi apparatus, and ER-Golgi intermediate compartment (ERGIC), an intervening membrane complex identified in mammalian cells (Appenzeller-Herzog and Hauri, 2006; Saraste and Marie, 2018). In the 1960s, scientists led by George Palade identified the ER-Golgi system as the key regulatory site for secretion (Gomez-Navarro and Miller, 2016; Sabatini, 1999; Zanetti et al., 2011). In those early days, research mainly focused on the synthesis of secreted and transmembrane proteins and their movements within the ER-Golgi system. These studies led to the identification of vesicle carriers, including COPII- and COPI-coated vesicles, which mediate anterograde and retrograde transport (Gomez-Navarro and Miller, 2016). In addition, protein translocation pathways, such as SRP-SEC61-mediated protein translocation and the GET/TRC pathway for insertion of tail-anchored membrane proteins, were identified and characterized (Chio et al., 2017; Lang et al., 2017). As research went on, scientists found that the ER-Golgi system is not a simple series of compartments acting sequentially for protein delivery, but also for lipid synthesis and biogenesis of other organelles, such as autophagosomes and peroxisomes (Dimitrov et al., 2013; Jacquemyn et al., 2017; Nakatogawa, 2020; Sun et al., 2021). The multiple functions of the ER-Golgi system are controlled by sophisticated communication and exchanges coordinated through vesicle trafficking and membrane contacts (De Matteis and Rega, 2015; Venditti et al., 2020).

### *Anterograde secretory traffic*

A major role of the ER-Golgi system is secretory trafficking (Palade, 1975). Proteins destined to be secreted are inserted into the ER lumen through the SRP-SEC61 translocation system (Lang et al., 2017). Prior to their transport out of the ER, secretory cargoes are collected into special ER regions called ER-exit sites (ERESs) (Bannykh et al., 1996). In ERESs, the COPII coating machinery is required for anterograde trafficking of cargoes to the ERGIC (in vertebrate cells) or directly to the Golgi (in animals and eukaryotes other than vertebrates) (Jensen and Schekman, 2011). COPI-coated vesicles are generated from the ERGIC/Golgi to mediate intra-Golgi and retrograde transport to the ER for the purpose of recycling traffic regulators and retrieving escaped ER proteins (Orci et al., 1997). Detailed summaries of cargo sorting and COPII and COPI vesicle formation can be found elsewhere (Barlowe and Miller, 2013; Brandizzi and Barlowe, 2013; Gomez-Navarro and Miller, 2016; Peotter et al., 2019; Zanetti et al., 2011). Recent findings emphasize the importance of close, dynamic ER-ERGIC-Golgi association for cargo secretion.

Two proteins required in secretion have received a great deal of attention in recent years due to their role in maintaining the association between ERES and post-ERES (ERGIC or Golgi) membranes: Trk-fused gene (TFG) and Transport and Golgi organization 1 (Tango1). The role of TFG in ER-Golgi trafficking was identified by the Audhya group (Witte et al., 2011). The initial study revealed TFG as a protein that interacts with SEC16, which localizes to ERES and regulates COPII-mediated protein transport. Subsequent work showed that TFG forms oligomers that hold together ERES and ERGIC and help concentrate COPII-coated membranes at the ERES-ERGIC interface through its interaction with COPII coat protein SEC23 (Hanna et al., 2017; Johnson et al., 2015). On the other hand, TANGO1, identified in the Malhotra laboratory, is an ERES-localized transmembrane protein (Bard et al., 2006). TANGO1 contains an SH3 protein-protein interaction domain in its ER-luminal side that is postulated to bind cargoes or cargo adaptors (Saito et al., 2009). In the cytoplasmic part of TANGO1, multiple interactions have been mapped, including self-interaction to form oligomers and interactions with SEC16, SEC23, RAB1, and *cis*-Golgi proteins GRASP65 and GM130 (Feng et al., 2021; Maeda et al., 2017; Pang et al., 2022; Saito et al., 2009). Through its cytoplasmic interactions, TANGO1 and closely related proteins cTAGE5 and TALI define the ERES and tether it to the ERGIC/Golgi. In the absence of TANGO1, ERESs in *Drosophila* ERES-Golgi units become smaller and uncouple from the Golgi (Liu et al., 2017), indicating that TANGO1 is essential to maintaining the ER-Golgi association (Figure 2, i).

Notably, despite both TFG and Tango1 affecting general secretion, their effects are most strongly noticed in the secretion of collagen (Liu et al., 2017; McCaughey et al., 2016; Saito et al., 2009). Collagens are rods 300–400 nm long, making it impossible to fit into the 60–80 nm vesicles that COPII produces *in vitro* (Barlowe et al., 1994; Fromme and Schekman, 2005; Malhotra and Erlmann, 2015). The requirement of TFG and Tango1 in collagen secretion has been interpreted to stem from an involvement of the ERES-ERGIC/Golgi association in the building of enlarged vesicle megacarriers capable of transporting large cargoes. These hypothetical megacarriers would be formed due to membrane delivery from the ERGIC to growing COPII vesicles (Santos et al., 2015). However, an alternative is a direct tubular connection between ERES and ERGIC/Golgi mediating the anterograde traffic of cargoes, both large and small, in addition to regular-sized COPII vesicles, or instead of them (Raote and Malhotra, 2021). According to two recent studies, rather than mediating vesicle budding, COPII localizes to a narrow neck region between the ER and ERES, where it serves in a gating role for cargo concentration (Shomron et al., 2021; Weigel et al., 2021). According to FIB-SEM observations in cultured human cells, the ERES is a tubular network from which very long (2.4 μm on average) tubular carriers protrude, directly connecting the ERES and ERGIC (Weigel et al., 2021) (Figure 2, i). The formation and movement of these tubes would be dependent not on COPII, but on Rab1 (Shomron et al., 2021; Westrate et al., 2020) and COPI (Weigel et al., 2021). Questions remain about the role of COPII and COPI, as these findings imply a significant departure from extant conceptions of how ER-Golgi traffic operates and conflict with observations of COPII vesicles in cells (Bykov et al., 2017; Hughes et al., 2009; Zeuschner et al., 2006). In addition, the overexpression of tagged COPII proteins and the RUSH system for synchronic cargo release could be sources of artifacts in these studies. However, direct ER-Golgi association has been observed in yeast, where dynamic kiss-and-run

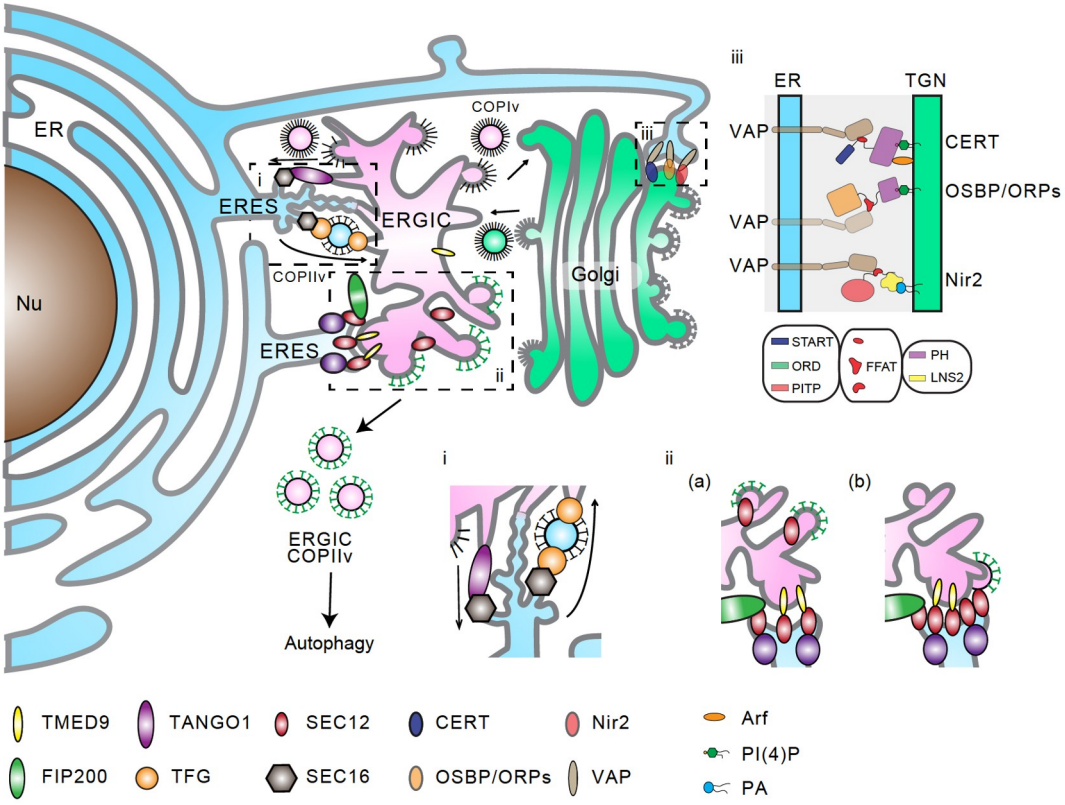



**Figure 2.** Membrane associations and contacts in the ER-Golgi system. i, Under steady states, the ERES associates with the ERGIC/Golgi for secretory protein trafficking. The TFG oligomer maintains the ERES-ERGIC association and tethers COPII vesicles for correct targeting to the ERGIC/Golgi. TANGO1 and closely related proteins cTAGE5 and TALI (simplified as TANGO1) interact with multiple ERES proteins, maintain ERES size, and tether ERES to the ERGIC/Golgi. ii, Under stress conditions, the ERES is enlarged, which is dependent on the FIP200-SEC12 association. ERES enlargement facilitates establishment of the ERGIC-ERES membrane contact mediated by the TMED9-SEC12 interaction. The contact enables SEC12 to transactivate COPII vesicle formation on the ERGIC. In addition, SEC12 translocates to the ERGIC and activates cis ERGIC-COPII formation. Through both mechanisms, ERGIC-COPII can be generated and act as an autophagic membrane precursor. iii, The ER forms a contact with TGN. The contact is maintained by structural and lipid transfer proteins. Three lipid transfer proteins are listed, including CERT, OSBP/ORPs, and Nir2. They contain the FFAT motif that allows them to associate with VAP protein on the ER and a lipid binding motif that interacts with lipids on the Golgi. Through the two motifs, the proteins are able to localize to the ER-TGN contact interface. In addition, the proteins contain lipid binding domains that could facilitate non-vesicular lipid transport between the ER and TGN.

interactions between the ERES and *cis*-Golgi are involved in cargo transfer (Kurokawa et al., 2014). Furthermore, a direct tubular connection between the ERES and Golgi has been documented by FIB-SEM in *Drosophila*, where the distance between an ERES and Golgi is only about 100–200 nm (Yang et al., 2021). Overall, it is increasingly clear that secretory traffic involves more than the emission of vesicles by the ERES, and that tight ER-ERGIC/Golgi contact, exchange, and physical coupling are essential for efficient ER-Golgi trafficking.

## *Autophagosome generation*

In addition to mediating membrane trafficking, the ER-Golgi system has been shown to regulate autophagy, an essential catabolic cellular process mediated by bulk degradation of cytoplasmic components through the lysosome (Nakatogawa, 2020). A key characteristic of autophagy is the formation of double-membrane autophagosomes, which encapsulate cytoplasmic cargoes and deliver them to the lysosome. Formation of the autophagosome is a sophisticated process that requires remodeling of the endomembrane system to generate autophagosome membrane precursors. These precursors first assemble into a phagophore, a cup-shaped precursor of the autophagosome, in a special location called the phagophore assembly site (PAS) (Nakatogawa, 2020). Lipid transfer and *de novo* synthesis also contribute to autophagosome biogenesis. Detailed descriptions of autophagosome biogenesis have been provided elsewhere (Morishita and Mizushima, 2019; Nakatogawa, 2020).

How the endomembrane system reorganizes to generate autophagosome precursors has been a puzzle for decades. Recent evidence indicates that the ER-Golgi system is remodeled under stress conditions to form a new type of membrane contact, the ERGIC-ERES contact, essential for the generation of early autophagosome precursors (Ge et al., 2017; Li et al., 2022b) (Figure 2, ii). Stress-induced remodeling of ERES has been reported by several groups, including the formation of SEC16 liquid phase granules in *Drosophila* cells (Zacharogianni et al., 2014) and increased duration of the ERES-cis-Golgi association in yeast (Kurokawa et al., 2014). A major purpose of ERES alteration has been proposed to be the inhibition of protein secretion, but other functions are likely. In mammalian cells, starvation induces enlargement of the ERES, which leads to a tight association with the ERGIC (Ge et al., 2017). Interestingly, enlargement of the ERES is dependent on FIP200, an autophagy-related gene (ATG) protein (Ge et al., 2017) shown to be part of the ULK1 kinase complex and to act in the early step of autophagy at the PAS (Mizushima et al., 2011). However, in the process of ERES remodeling, FIP200 associates with SEC12, an

ERES-localized GEF, to initiate COPII assembly instead of acting in the ULK1 kinase complex (Ge et al., 2017; Gomez-Navarro and Miller, 2016; Zanetti et al., 2011). The prevention of starvation-induced ERES remodeling by interfering with the FIP200-SEC12 association inhibits autophagosome biogenesis (Ge et al., 2017).

How does ERES remodeling affect autophagosome biogenesis? Electron tomography analysis indicates that the ERGIC and ERES form an MCS under starvation conditions with very short distance (as close as 2–5 nm). The contact is mediated by the interaction between ERES-localized SEC12 and ERGIC-localized TMED9 protein. Because the cytosolic diameter of SEC12 is ~5 nm, the short distance between the ERGIC and ERES allows for ERES-localized SEC12 to physically reach the ERGIC membrane (Li et al., 2022b). As mentioned above, SEC12 is an initiator of COPII vesicle formation. The contact of SEC12 with the ERGIC enables transactivation of the COPII assembly on the ERGIC. In addition, this short distance allows the relocation of SEC12 to the ERGIC through an unknown but likely membrane fusion-independent mechanism. The relocated ERGIC-SEC12 could also trigger COPII formation on the ERGIC (Li et al., 2022b). Through both mechanisms, ERGIC-ERES contact promotes the formation of a special type of COPII vesicle on the ERGIC, the ERGIC-COPII vesicle, which specifically functions as a membrane template for LC3 lipidation, a key step in autophagosome biogenesis (Ge et al., 2013; Ge et al., 2014; Li et al., 2022b). Of the whole process, remodeling of the ERES is essential because depletion of FIP200 abolishes ERES enlargement, ERGIC-ERES formation, and autophagosome biogenesis (Ge et al., 2017; Li et al., 2022b). These studies indicate that the function of the ER-Golgi system could be redirected by autophagic factors, such as FIP200. Through ERGIC-ERES contact formation, the site of COPII assembly is relocated from the ERES to the ERGIC, accompanying COPII's functional switch from membrane trafficking to autophagy (Figure 2, ii). Therefore, ERGIC-ERES contact formation serves as a mechanism for the functional shift of the ER-Golgi system under stress conditions.

### *Control of lipid transport and synthesis*

The vesicular trafficking of secretory cargoes in the ER-Golgi system is directional, i.e., through the ER, ERGIC, *cis*-Golgi, and *trans*-Golgi network (TGN) (Gomez-Navarro and Miller, 2016; Zanetti et al., 2011). Sequential delivery requires associations between adjacent compartments. Interestingly, evidence indicates that physical interactions also occur between compartments that are non-adjacent in principle in the ER-Golgi system, such as the ER and TGN (De Matteis and Rega, 2015; Venditti et al., 2020).

ER-TGN contact sites were first observed in the 1960s by electron microscopy but lacked further characterization until the identification of ceramide transfer protein CERT in studies of sphingomyelin synthesis (De Matteis and Rega, 2015; Hanada et al., 2003). CERT contains an FFAT motif to interact with VAPs on the ER and a pleckstrin homology (PH) domain to bind phosphatidylinositol-4 phosphate (PI4P) and ARF1 on the TGN (Kumagai et al., 2007). In addition, CERT contains a steroidogenic acute regulatory protein (StAR)-related lipid transfer (StART) domain that is able to bind and transfer ceramide. Through its three functional domains, CERT localizes to ER-TGN contact sites and mediates ceramide transport from the ER to the TGN through non-vesicular trafficking (Hanada et al., 2003; Kumagai et al., 2007) (Figure 2, iii). Once in the TGN, ceramide serves as a substrate for sphingomyelin synthesis mediated by sphingomyelin synthase 1 (Fukasawa et al., 1999; Hanada et al., 2003; Kumagai et al., 2007).

CERT is not the only case of lipid transfer at ER-TGN contact sites. Multiple lipid transfer proteins have been identified, including oxysterol-binding protein (OSBP), OSBP-related proteins (ORP9, 10, 11, and 4L), Nir2, and FAPP2 (Litvak et al., 2005; Maeda et al., 2013; Mesmin et al., 2013; Ngo and Ridgway, 2009; Pietrangelo and Ridgway, 2018; Venditti et al., 2019b). Similar to CERT, they contain FFAT motifs and PH domains for correct targeting to the ER-TGN contact interface, except Nir2 contains a Lipin/Ned1/Smp2 (LNS2) domain instead of PH and binds to PA on the TGN (Masone et al., 2019). The proteins also contain lipid transfer domains, such as OSBP-related domain (ORD) for OSBP and ORPs, glycolipid transfer protein (GLTP) domain for FAPP2, and phosphatidylinositol transfer protein (PITP) for Nir2, which allows the transfer of lipids, including sterols, phospholipids, and glucosylceramide, from the ER to the TGN (Masone et al., 2019; Venditti et al., 2020) (Figure 2, iii). Regarding the mechanism of lipid transfer, a lipid exchange model has been proposed for OSBP in which sterols are transported from the ER to the TGN, followed by a back transfer of PI4P from the TGN to the ER. On the ER, PI4P is hydrolyzed to phosphatidylinositol (PI) by the lipid phosphatase SAC1. Therefore, the counter gradient transport of sterols is fueled by PI4P hydrolysis and negative feedback occurs when the PI4P level decreases on the TGN (Mesmin et al., 2013).

Electron tomographic analysis has indicated a tight association (~5–20 nm distance) between apposed membranes at ER-TGN contact sites (Venditti et al., 2019b). This distance is closer than other types of membrane contacts, such as ER-mito (10–30 nm) and ER-PM (10–30 nm) (Chang et al., 2017; Xu et al., 2020). This short distance likely ensures efficient lipid exchange mediated by multiple lipid transfer proteins. In addition, similar to ERGIC-ERES contact sites, such tight apposition enables ER-localized SAC1 to hydrolyze PI4P on the TGN *in trans* to control PI4P levels (Venditti et al., 2019a). The membrane contact between the ER and TGN is maintained by several lipid transfer proteins (e.g., OSBP and ORP10) (Venditti et al., 2020; Venditti et al., 2019b). Moreover, scaffold proteins and adaptors (e.g., ACBD3 and FAPP1) are involved in establishing contact and targeting protein factors to the contact site (Shinoda et al., 2012; Venditti et al., 2019a).

## ER-endosome contact

Endocytosis mediates the uptake of exterior material into the cell via inward budding of the PM. Endocytosed cargoes are initially found in early endosomes (EEs), which gradually mature into late endosomes (LEs). From these compartments, cargoes can be sorted to different destinations—back to the PM, into intraluminal vesicles (ILVs) for trafficking to lysosomes, or to the biosynthetic pathway (Huotari and Helenius, 2011). Extended MCSs between the ER and endosomes have recently been revealed in many cell types (Di Mattia et al., 2020) (Figure 3). Intriguingly, such contacts become increasingly abundant as endosomes mature (Friedman et al., 2013). Although morphologically similar, different ER-endosome contact sites have distinct molecular compositions and functions. Currently known molecular architectures of ER-endosome MCSs in mammalian

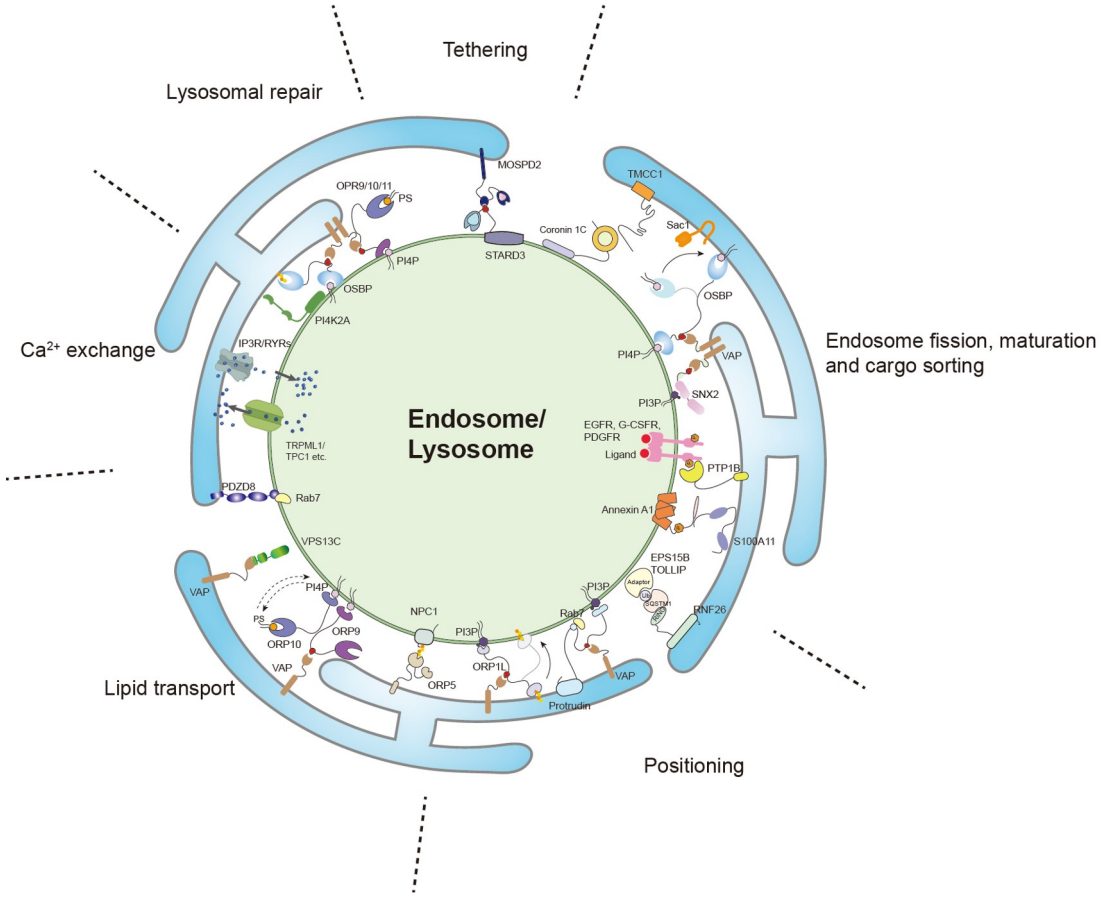



**Figure 3.** ER-endosome/lysosome contact sites and their functions. The ER-endo/lysosome contact sites have diverse functions, including regulating endo/lysosome positioning and maturation, maintaining membrane integrity, and mediating material exchange. Contact sites established by TMCC1 and Coronin 1C facilitate the recruitment of ER tubules to promote endosome fission and cargo sorting. Contact sites involving VAP/SNX2/OSBP regulate endosome motility and endosome-to-Golgi traffic by transporting PI4P from endosomes to the ER, which enables the degradation of PI4P by the ER-localized phosphatase Sac1. The Annexin A1 and S100A11 interaction reinforces ER-MVB contact sites, which play an important role in sorting endocytosed receptors into ILVs. The ubiquitin ligase RNF26, along with scaffold protein SQSTM1 and ubiquitin binding domain-containing proteins associated with endosomal compartments, governs the perinuclear positioning of endo/lysosomes. ORP1L/VAP and Protrudin/VAP contact sites control the movement of endo/lysosomes along microtubules. NPC1/ORP5 and ORP1L/VAP contact sites regulate cholesterol egress from endo/lysosomes. Another lipid transfer protein, ORP10, localized at the ER-endo/lysosome contacts tethered by ORP9 and VAP, supplies PS in exchange for PI4P to endosomes. Lipid transfer processes at the ER-endo/lysosome contact sites are also mediated by the VPS13 family proteins. Contact sites consisting of TPCs and IP3Rs/RyRs regulate the release of $Ca^{2+}$ from lysosomes and ER. Upon lysosomal membrane permeabilization, PI4K2A rapidly accumulates on damaged lysosomes, producing PI4P. It recruits multiple members of the ORP family, facilitating the robust transfer of PS and cholesterol from ER to support lysosomal repair. Interactions involving PDZD8 (Guillén-Samander et al., 2019; Hirabayashi et al., 2017; Shirane et al., 2020) and Rab7, as well as MOSPD2 (Di Mattia et al., 2018) and STARD3 (Alpy et al., 2013), also promote the formation of ER-endo/lysosome contact sites.

cells and their associated functions are provided in Figure 3.

## *Endosome positioning*

The dynamic movements of endosomes within the cytosol are mediated by the recruitment of adaptor proteins that link endosomes with microtubule motors. Adaptor recruitment and the direction of endosome trafficking on microtubules are modulated by ER-endosome MCSs and coupled to the metabolic state of the cell. ER-LE contact sites established by the interaction of LE-localized ORP1L and ER-localized VAPs control the motility of LEs along microtubules (Johansson et al., 2007; Rocha et al., 2009). ORP1L, which belongs to the OSBP-related protein (ORP) family, harbors an FFAT motif and a C-terminal lipid binding domain. The ORP1L-VAP interaction relies on the sensing of endosomal cholesterol levels by ORP1L. Under high cholesterol levels, ORP1L binds the small GTPase Rab7 and promotes the association of Rab7 effector RILP with the dynein-dynactin motor, which favors the retrograde transport of LEs. Alternatively, under low cholesterol levels, ORP1L undergoes a conformation change that exposes its FFAT motif and allows it to bind VAP, resulting in the formation of ER-LE contacts. Such interaction causes the dynein motor to dissociate from the Rab7-RILP complex on the LE surface and impairs trafficking of LEs to the cell center.

The ER membrane protein protrudin, which functions at ER-LE contact sites, also controls the motility of LEs (Raiborg et al., 2015). Similar to ORP1L, protrudin contains an FFAT motif that binds VAPs. Protrudin induces the formation of contact sites, likely through detection of Rab7-GTP and the endosomal lipid phosphatidylinositol-3 phosphate (PI3P) (Pedersen et al., 2020). The protrudin-VAP complex facilitates the transfer of kinesin-1, a microtubule motor, from protrudin to FYCO1 on LEs, which in turn promotes anterograde trafficking of LEs (Pankiv et al., 2010). Consistently, LEs move to the cell periphery in protrudin-expressing cells, but they accumulate in the perinuclear region when protrudin, kinesin-1, or FYCO1 is depleted. Fusion of the FYCO1-containing LEs with the PM promotes outgrowth of

protrusions and neurites (Raiborg et al., 2015). Protrudin-mediated LE trafficking also facilitates the activation of major metabolism regulator mTORC1. Whether the protrudin- and ORP1L-containing contact sites coordinately regulate LE positioning in response to changes in cholesterol and nutrient levels is worth further study.

The ER-anchored ubiquitin ligase RING finger protein 26 (RNF26) has also been shown to control the spatiotemporal organization of endosomes (Jongsma et al., 2016). RNF26 interacts and ubiquitinates SQSTM1, which in turn recruits several ubiquitin binding domain-containing proteins associated with endosomal compartments, such as the EE protein EPS15 and LE protein TOLLIP. These interactions function to restrain endosomes near the perinuclear region.

ER-endosome contacts also play a critical role in shaping the ER network. Time lapse imaging has revealed that endosomes remain bound to the tubular ER as they traffic, which causes the ER to wrap around them (Friedman et al., 2013). Furthermore, co-migration of the ER with endosomes, preferentially Rab7-marked LEs and lysosomes, was recently demonstrated to be a key mechanism controlling ER network architecture (Spits et al., 2021). Conditions restricting LE movement, such as cell starvation or depletion of contact proteins, significantly reduce ER dynamics and the complexity of the ER network.

## Endosome fission and cargo sorting

ER-endosome contacts regulate the location and timing of endosome fission, which is important for endosome maturation and cargo sorting (Rowland et al., 2014). Several contact proteins have been implicated in this process. TMCC1, an ER membrane protein, coordinates with endosomal Coronin 1C to recruit ER tubules to the endosome fission sites marked by FAM21, a retromer-associated protein and subunit of the WASH complex (Hoyer et al., 2018). Depletion of either TMCC1 or Coronin 1C reduces the number of FAM21-labeled ER-associated endosome buds and consequently impairs fission. A complex assembled between Spastin, the microtubule-severing ATPase, and IST1, a component of the endosomal sorting complex required for transport (ESCRT)-III machinery, has been shown to regulate endosome fission at the ER-endosome contact sites (Allison et al., 2017; Allison et al., 2013). Spastin associates with the ER by interacting with several ER-shaping proteins. Depletion of Spastin or IST1 or expressing an ATPase-defective Spastin results in an increase in the lifetime of endosome tubulation. A direct physical link between VAPs and the retromer component SNX2 has also been suggested to promote endosome fission (Dong et al., 2016).

ER-facilitated endosome fission could regulate cargo sorting. EEs that have been contacted by ER tubules consist of segregated domains for anterograde trafficking and recycling, which are marked by Rab5 and Rab4, respectively (Sonnichsen et al., 2000). Tubules originating from EEs and LEs sort a number of proteins, including the mannose 6-phosphate receptor (M6PR), for recycling away from the lysosomal pathway. The TMCC1/Coronin 1C, Spastin/IST1, and VAP/SNX2 contacts all have been implicated in the retrieval of M6PR (Allison et al., 2017; Dong et al., 2016; Hoyer et al., 2018). The contacts formed by Reticulon-3L, an ER-localized reticulon family protein, and Rab9a, an endosomal protein, were recently discovered to function in endosome maturation as well as cargo sorting (Wu and Voeltz, 2021). Whether this activity involves endosome fission needs further investigation.

ER-endosome contacts could also directly regulate cargo sorting. Contacts between the ER and multivesicular bodies (MVBs) help sort the epidermal growth factor receptors (EGFRs). After ligand binding and activation, phosphorylated EGFRs are rapidly endocytosed and dephosphorylated by PTP1B, an ER-localized phosphatase (Eden et al., 2010). Dephosphorylation occurs at the ER-MVB contact sites, which leads to the sorting of EGFR into ILVs and subsequent degradation (Eden et al., 2010). A number of other receptor tyrosine kinases are also subjected to PTP1B-dependent dephosphorylation (Haj et al., 2002; Palande et al., 2011). The contacts between EGFR-containing MVBs and the ER are reinforced by an interaction of Annexin A1, an endosomal EGFR substrate, with ER protein S100A11 (Eden et al., 2016). Depletion of PTP1B, Annexin A1, or S100A11 similarly decreases the number of contact sites and prolongs EGFR phosphorylation, and EGFR dephosphorylation induced by overexpression of PTP1B is suppressed by loss of Annexin A1 (Eden et al., 2016). Furthermore, Annexin A1/S100A11 and PTP1B mediate the dephosphorylation of components of the ESCRT-0 complex, which has also been suggested to control the formation of ILVs (Eden et al., 2010; Stuible et al., 2010).

## Lipid and calcium transport

ER-endosome contacts have been shown to facilitate lipid and $Ca^{2+}$ exchange between the two organelles. Cholesterol is probably the best-documented lipid transferred at ER-endosome contact sites. In addition to *de novo* synthesis, cells acquire cholesterol through endocytosis of low-density lipoprotein (LDL) particles. Endocytosed LDL is hydrolyzed into unesterified cholesterol in the lumen of LEs, which is then transferred to the membrane-associated transporter NPC1 (Luo et al., 2019, Li et al., 2022a). The NPC1/ORP5 and ORP1L/VAP contacts have been suggested to facilitate cholesterol egress from LEs. ORP5, an integral ER membrane protein, forms contacts with LEs by interacting with NPC1 (Du et al., 2011). Such interaction appears to mediate cholesterol export from LEs to the ER membrane, likely by shuttling via the cholesterol binding domain of ORP5 (Du et al., 2011). Consistently, depletion of ORP5 causes cholesterol accumulation on the LE membrane. The presence of a lipid binding domain in ORP1L makes it another suitable candidate for transferring cholesterol between the two organelles (Vihervaara et al., 2011) (Figure 3). ORP1L-deficient cells present cholesterol transfer defects, including reduced cholesterol esterification in the ER, increased expression of sterol-regulated genes, increased cholesterol and fatty acid biosynthesis, and cholesterol accumulation on endosomes (Zhao and Ridgway, 2017). Cholesterol can be transferred in a reverse direction from the ER to endosomes. Interestingly, ORP1L has also been implicated in this process. Depriving cells of LDL have been shown to recruit ORP1L to the Annexin A1-marked ER-MVB contact sites, which promotes the transport of ER-derived cholesterol to MVBs and the formation of ILVs (Eden et al., 2016). Furthermore, ORP1L depletion results in the formation of enlarged endosomes containing fewer ILVs. However, this function appears to contradict the aforementioned role of ORP1L in endosome-to-ER cholesterol transport (Zhao and Ridgway, 2017). Thus, studies are needed to resolve this paradox.

In addition to the ORP1L/VAP contact, MCSs involving


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STARD3 and VAP mediate cholesterol transport from the ER to LEs (Wilhelm et al., 2017). STARD3 is composed of an N-terminal MENTAL domain, which anchors the protein on LEs, a C-terminal START domain, which is capable of binding cholesterol, and an FFAT-like motif. Both a functional START domain and the ability to interact with VAPs are required for cholesterol transport activity. Overexpression of STARD3 has been shown to induce cholesterol accumulation in LEs by rerouting newly synthesized cholesterol to LEs, leading to a reduction in cholesterol levels in the PM. Similar to ORP1L, STARD3 seems to play a role in the biogenesis of ILVs.

Transferring phosphoinositides, particularly PI4P, also contributes to lipid homeostasis at ER-endosome contact sites. OSBP localizes at the contact sites built by VAPs and SNX2 (Dong et al., 2016). It regulates endosome-to-Golgi traffic by transporting PI4P from endosomes to the ER, which allows the ER-localized phosphatase Sac1 to subsequently degrade PI4P (Dong et al., 2016). In the absence of OSBP or VAP, PI4P accumulates on EEs and LEs, which leads to increased actin nucleation mediated by the WASH complex, altered endosomal motility, and reduced cargo recycling (Dong et al., 2016). OSBP has been shown to counter-exchange cholesterol and PI4P between the ER and Golgi (Mesmin et al., 2013). Whether it regulates PI4P levels on endosomes by counter-transporting cholesterol remains to be determined. ORP10, which localizes at the ER-endosome contact sites, tethered by ORP9 and VAP, has been shown to supply phosphatidylserine (PS) in exchange for PI4P to endosomes, where the PS-binding protein EHD1 is recruited to promote endosome fission (Kawasaki et al., 2022). In addition, transferring PI4P to the ER via ORP1L has been shown to regulate phagolysosome tubulation and resolution (Levin-Konigsberg et al., 2019).

Calcium exchange also occurs between the ER and endosomes. Similar to the ER, endosomes are $Ca^{2+}$ storage organelles that can be mobilized for localized $Ca^{2+}$ release. Endosomes release $Ca^{2+}$ through transient receptor potential channels (TRPs) and two-pore channels (TPCs). ER-endosome contact is regulated by local $Ca^{2+}$ release from endosomes (Kilpatrick et al., 2017). The TPC1 channel localizes at ER-endosome contact sites. TPC1 depletion decreases the frequency of contacts and impairs the accessibility of EGFR to PTP1B. Additional evidence indicates that $Ca^{2+}$ released via the IP3R on the ER could be sequestered into endosomes and lysosomes through yet unknown $Ca^{2+}$ channels (Lopez-Sanjurjo et al., 2013).

Though a number of ER-endosome contact sites with distinct molecular architectures and functions have been identified (Figure 3), and many more are likely to be discovered in the near future, how the cell orchestrates the formation and function of these MCSs requires further investigation. Whether different contact sites co-localize or occupy distinct domains and whether they coordinate with each other to carry out cellular functions is currently unclear.

## ER-lysosome contact

Lysosomes were initially considered specialized and isolated cytoplasmic organelles of eukaryotic cells. Their primary cellular function was thought to be the use of their approximately 60 luminal hydrolases to degrade biological macromolecules, such as proteins, lipids, carbohydrates, and nucleic acids, for recycling (Luzio et al., 2007; Xu and Ren, 2015). These macromolecules are delivered to lysosomes by various degradative pathways, including endocytosis, autophagy, and phagocytosis (Luzio et al., 2007; Xu and Ren, 2015). This isolated view of lysosomes has been fundamentally changed by reports of lysosomes acting as hubs for the regulation of cellular metabolism and the stress response (Ballabio and Bonifacino, 2020; Perera and Zoncu, 2016). To serve their diverse cellular functions, lysosomes interact extensively with other membrane-bound intracellular organelles to coordinate and integrate specialized organelle functions (Li et al., 2021a). Specifically, lysosomes interact continuously with each other through homotypic fusion and fusion with organelles (e.g., LEs, autophagosomes, and phagosomes) and the PM through heterotypic fusion (Ballabio and Bonifacino, 2020; Luzio et al., 2007). In addition, lysosomes interact transiently with organelles, such as the ER, Golgi apparatus, mitochondria, and peroxisomes, through membrane contacts (Figure 3) (Prinz et al., 2020; Scorrano et al., 2019).

The interactions of lysosomes with the ER, now recognized as a master regulator of membrane trafficking and the functions of most, if not all, intracellular organelles (Wenzel et al., 2022; Wu et al., 2018), are particularly important in mediating ER- and lysosome-associated cellular functions. These interactions are initiated and executed by ER-lysosome MCSs (Figure 3) (Prinz et al., 2020; Scorrano et al., 2019). As discussed above, membrane contacts are ubiquitous among intracellular organelles (Shai et al., 2018; Valm et al., 2017), and MCSs play critical roles in a broad range of cellular functions, including membrane trafficking, intracellular signaling, metabolic regulation, stress response, and organelle biogenesis (Prinz et al., 2020). Thus, interactions of the ER with lysosomes through MCSs mediate a broad range of important cellular functions, including cellular metabolism, signal transduction, lysosomal damage repair, lysosomal positioning and motility, and organelle dynamics. Dysfunction of lysosomal MCSs has been implicated in various human diseases, including lysosomal storage diseases, neurodegenerative diseases, and metabolic disorders (Ballabio and Bonifacino, 2020; Guillén-Samander and De Camilli, 2023; Kim et al., 2022; Parenti et al., 2015; Prinz et al., 2020).

### *Metabolite transport and metabolic regulation*

A primary cellular function mediated by ER-lysosome contact sites is the transport of metabolites, such as cholesterol and lipids, between the two organelles, a process essential to cellular metabolism and homeostasis (Lawrence and Zoncu, 2019; Luo et al., 2017; Prinz et al., 2020). Cholesterol is transported between the ER and lysosomes (Figure 3) by the same set of proteins that mediate its traffic between the ER and endosomes. VPS13C of the VPS protein family (Ugur et al., 2020) was recently found to provide another pathway for metabolite transport. It is recruited by lysosomal protein Rab7 to ER-lysosome contact sites and interacts with VAP to transfer phospholipids (Figure 3) (Hancock-Cerutti et al., 2022; Kumar et al., 2018). Overall, the coexistence of multiple metabolite transport pathways that provide functional redundancy and individuality for direct material exchange between different organelles is observed in many types of MCSs (Prinz et al., 2020; Scorrano et al., 2019). Notably, because of frequent fusion and close association of lysosomes with LEs (Huotari and Helenius, 2011), the same MCS proteins are often identified for ER-lysosome and ER-endosome interactions despite differences in the function and composition

between lysosomes and endosomes.

Another primary cellular function mediated by ER-lysosome contact sites is the regulation of cellular metabolism. Because the primary function of lysosomes is to degrade and recycle cellular macromolecules, they are in a unique position to sense and regulate cellular metabolism (Ballabio and Bonifacino, 2020; Lawrence and Zoncu, 2019). When lysosomal membrane-anchored Rag GTPases are activated in response to amino acids, they promote translocation of the mTOR complex 1 (mTORC1) kinase, a master regulator of cellular growth, to the surface of lysosomes, where it becomes activated (Sancak et al., 2010; Zoncu et al., 2011). ER-lysosome contact sites have been found to provide a regulatory pathway for mTORC1 activity through cholesterol transport. Recruitment and activation of mTORC1 to the lysosomal surface require lysosomal cholesterol (Castellano Brian et al., 2017). The transfer of cholesterol from the ER to lysosomes by OSBP in cooperation with VAP (Figure 3) is critical for further activation of mTORC1 (Dong et al., 2016; Mesmin et al., 2017). OSBP-VAP-mediated cholesterol transport drives constitutive activation of mTORC1 in a Niemann-Pick type C disease model caused by the loss of lysosomal cholesterol transporter NPC1, a negative regulator of the number of ER-lysosome MCSs and sterol transport activity of the OSBP-VAP machinery (Figure 3) (Lim et al., 2019). Overall, the cholesterol level-mediated activation of mTORC1 is balanced by different cholesterol transport mechanisms that converge at ER-lysosome MCSs.

## $Ca^{2+}$ exchange for cellular signaling

In addition to cellular metabolism, ER-lysosome contact sites also play critical roles in cellular signaling. An important function of ER-lysosome MCSs is the exchange of signaling factors, such as $Ca^{2+}$. Though the ER is a primary storage compartment for $Ca^{2+}$, lysosomes are highly acidic, mobilizable $Ca^{2+}$ stores (Berridge et al., 2000; Kilpatrick et al., 2013; Morgan et al., 2011). In the "trigger hypothesis" of nicotinic acid adenine dinucleotide phosphate (NAADP)-mediated $Ca^{2+}$ signaling, NAADP, the most potent $Ca^{2+}$ mobilizing second messenger, evokes release from lysosomal $Ca^{2+}$ stores, which further triggers substantial $Ca^{2+}$ release from the ER (Cancela et al., 1999; Galione et al., 2010). ER-lysosome contact sites enable physical and functional coupling between the ER and lysosome as two major intracellular $Ca^{2+}$ stores and stimulate spatiotemporally complex $Ca^{2+}$ signaling (Cancela et al., 1999). Specifically, NAADP evokes acidic $Ca^{2+}$ release by activating TPCs, lysosomal $Ca^{2+}$ channels at the ER-lysosome contact sites (Figure 3) (Jha et al., 2014; Wang et al., 2012), and activated TPCs then stabilize the MCSs (Kilpatrick et al., 2017). Lysosomal $Ca^{2+}$ signaling can be amplified by IP3Rs or ryanodine receptors (RyRs) in closely apposed ER regions (Figure 3) (Mikoshiba, 1997; Van Petegem, 2012). $IP_3Rs$ form clusters or puncta on the ER membrane and preferentially associate with lysosomes to selectively transport $Ca^{2+}$ from the ER to lysosomes (Atakpa et al., 2018). Notably, TPCs and $IP_3Rs$ colocalize and associate with MCSs but do not directly contribute to the formation of MCSs as tether proteins. $Ca^{2+}$ transport through ER-lysosome contact sites seems to be bidirectional. $IP_3R$-evoked $Ca^{2+}$ signals can be rapidly loaded onto lysosomes to activate NAADP, as well as TPCs (Morgan et al., 2013), and to further control endocytic fusion and fission, autophagy, and lysosomal biogenesis (Medina et al., 2015; Ruas et al., 2010). NAADP-TPC-induced $Ca^{2+}$ release at lysosomes also triggers the activation of RyRs in muscle cells and pancreatic acinar cells (Gerasimenko et al., 2015; Kelu et al., 2017; Protasi, 2002), and type III RyRs colocalize predominantly with lysosomes in rat arterial smooth muscle cells (Kinnear et al., 2008). However, the tether and transport machinery that couples and amplifies lysosomal and ER $Ca^{2+}$ release at the MCSs remain to be elucidated.

## Rapid lysosomal repair

Under normal conditions, lysosomes maintain a highly acidic lumen with a pH of 4.5–5.0 and high levels of digestive enzymes. However, when the lysosomal membrane is damaged by various forms of physical, chemical, or pathogenic insults (Zoncu and Perera, 2022), the lysosomal contents are released into the cytosol, a condition termed lysosomal membrane permeabilization (LMP) (Wang et al., 2018). LMP must be repaired quickly because leaked luminal components, such as cathepsins, can induce cell death (Wang et al., 2018). Two studies (Radulovic et al., 2018; Skowyra et al., 2018) found that, upon acute but limited membrane damage, release of lysosomal $Ca^{2+}$ rapidly triggers recruitment of ESCRT (Vietri et al., 2020) proteins to initiate a repair program. However, if the damage exceeds the repair capacity of ESCRT, exposure of luminal glycoproteins triggers recruitment of the carbohydrate-binding proteins galectins (Johannes et al., 2018). Galectins work together with a variety of additional proteins, such as E3 ubiquitin ligases and autophagy cargo receptors, to initiate a clearance program through selective autophagy of lysosomes, also called lysophagy (Chauhan et al., 2016; Eapen et al., 2021; Maejima et al., 2013).

The depletion of ESCRT only partially blocks the repair of damaged lysosomal membranes, which suggests the existence of other repair mechanisms. A new lysosomal repair pathway mediated by ER-lysosome interactions was recently identified (Tan and Finkel, 2022). Specifically, upon LMP, phosphatidylinositol-4 kinase type 2α (PI4K2A) rapidly accumulates on damaged lysosomes and directly phosphorylates PI to produce lipid messenger PI4P, which then recruits multiple members of the ORP family, including ORP9, ORP10, ORP11, and OSBP (Figure 3). Together, these proteins drive the formation of extensive new MCSs between damaged lysosomes and the ER. The ORPs then promote robust ER-to-lysosome transfer of PS and cholesterol to support rapid lysosomal repair. In addition, lipid transfer protein ATG2 is recruited to damaged lysosomes and becomes functionally stimulated by PS to mediate rapid membrane repair through direct lysosomal lipid transfer. Thus, ER-lysosome interactions are important in the rapid repair of lysosomal membrane damage.

## Positioning and movement of lysosomes

The important functions of ER-lysosome interactions via their MCSs in cellular metabolism and signaling, as well as lysosomal repair, require the lysosomes to be properly positioned (Ballabio and Bonifacino, 2020; Pu et al., 2016). Lysosomes are remarkably dynamic yet spatially organized cytoplasmic organelles (Ba et al., 2018; Li et al., 2021a). Under normal conditions, a substantial fraction of lysosomes form clusters and exhibit higher spatial densities in the perinuclear region, whereas others spread into the cell periphery, with some approaching the PM.


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Long-range positioning and bidirectional movement of lysosomes in the cytoplasm are driven by molecular motors walking on microtubules. Specifically, inward movement of lysosomes towards the perinuclear region is driven by cytoplasmic dynein with its cofactor dynactin (Burkhardt et al., 1997; Harada et al., 1998), whereas outward movement of lysosomes towards the cell periphery is driven by members of several kinesin families, including kinesin 1 on central microtubules and kinesin 2 on peripheral microtubules (Guardia et al., 2016; Matsushita et al., 2004; Nakata and Hirokawa, 1995).

During their movement, most lysosomes remain tethered to the ER through their MCSs (Cabukusta and Neefjes, 2018; Pu et al., 2016). Consequently, the morphology of the ER network serves as an important constraint for the positioning and movement of lysosomes. High-speed super-resolution live-cell imaging has shown that ER-lysosome interactions stabilize the movement of lysosomes by confining their diffusive movement (Guo et al., 2018). Local condensation of the ER contributes to the dynamic clustering of lysosomes, which substantially enhances their heterotypic fusion because local transient elevation of the spatial densities of lysosomes increases their likelihood of moving into close proximity of each other and engaging in heterotypic fusion (Ba et al., 2018). Similar to endosomes, MCSs facilitate the coupling of molecular motors to lysosomes. Further details can be found elsewhere (Cabukusta and Neefjes, 2018; Pu et al., 2016). Overall, the convergence of key regulators of lysosomal positioning and movement with ER-lysosome MCSs provides important links between cellular metabolism and lysosomal positioning and movement.

### *Regulation of lysosomal fission/fusion and ER network dynamics*

There is growing evidence that ER-lysosome interactions influence the dynamics of both lysosomes and the ER network. ER-lysosome contact sites may be involved in regulating the fission or fusion dynamics of lysosomes. In cultured hippocampal neurons, membrane contacts between the ER tubules and lysosomes have been shown to regulate lysosomal fission and fusion (Özkan et al., 2021). For example, knockdown of ER-shaping protein reticulon and DP1 (Voeltz et al., 2006; Westrate et al., 2015) significantly reduces both the fission and fusion of lysosomes, though whether the reduction is directly and specifically caused by disruption of ER-lysosome contact sites remains to be determined (Özkan et al., 2021). In addition, several studies have shown that ER-lysosome contacts cause the rearrangement and regrowth of ER tubules (Friedman et al., 2013; Guo et al., 2018). Using chemical and optogenetic methods to reposition lysosomes, the positioning of lysosomes has been shown to actively regulate the local distribution and morphology of the ER network (Lu et al., 2020), though the molecular mechanism and machinery of the regulation remain unknown.

## ER-LD contact

LDs emerge from the ER, which harbors most of the lipid biosynthesis enzymes, particularly for triacylglycerol (TAG) biosynthesis (Gao et al., 2019b; Yao et al., 2022). Time-lapse high-resolution imaging of mammalian cells labeled with different organelle markers has shown that LDs maintain near continuous contact with the ER (Valm et al., 2017). Organelle contacts usually occur between two organelles with bilayer lipid membranes. Although the two organelles are tethered together, they do not fuse. LDs are organelles with a hydrophobic core and a phospholipid monolayer. They can form typical organelle-type non-fusion contacts with the ER (Figure 4). However, many studies of ER-LD contact sites have explored a state in which ER-LD contact is mediated by a continuous hemi-fused membrane bridge (Figure 4), or even by embedding LDs in the ER (Hugenroth and Bohnert, 2020; Salo et al., 2019).

### *Transfer of lipids and proteins*

Similar to other organelle MCSs, ER-LD contact sites facilitate lipid exchange. ORP5, a member of the OSBP-related lipid transfer protein family, localizes at ER-LD contact sites in oleate acid-treated HeLa cells and functions to exchange PI4P and PS between the ER and LD. In ORP5-deficient cells, there is more PI4P and less PS on LDs (Figure 4) (Du et al., 2020). The continuous nature of ER-LD contact also supports direct lipid

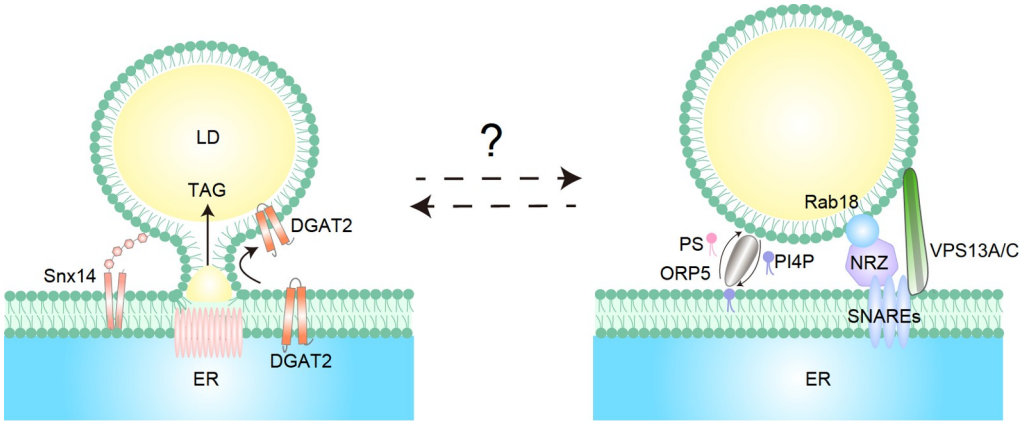



**Figure 4.** ER-LD contacts maintain lipid homeostasis through the transfer of lipids and proteins. LD biogenesis factors, including Seipin and Snx14, act at ER-LD contacts to support LD growth. The left panel shows continuous membrane contact between the ER and an LD, which supports the transfer of neutral lipids and membrane proteins in and out of LDs. The right panel shows protein-mediated contact between the ER and LD. Tethering factors, such as Rab18-NRZ/SNARE, establish the ER-LD contact. The dual-targeting lipid-transfer proteins ORP5 and Vps13A/C mediate lipid exchange between the ER and LDs. How ER-LD contacts transition between the two forms is currently unclear.

transfer. The contact sites are important for lipid transfer from ER to LDs, particularly for neutral lipids, resulting in a net flow of neutral lipids from the ER to LDs to facilitate the growth of small LDs (Salo et al., 2019). The transfer of lipids offsets the membrane distortion caused by neutral lipid accumulation in the ER and relieves ER stress associated with lipid imbalance or overload.

Unlike other organelle MCSs, ER-LD contact sites are also involved in membrane protein transport due to their continuous nature. Proteins may translocate from the bilayer phospholipid membrane of the ER to the monolayer phospholipid membrane of LDs or the other way around. The transfer of proteins is essential for lipid homeostasis, including lipid storage, lipid biosynthesis, and lipid breakdown. For example, only LD-localized DGAT2 is able to promote LD expansion (Figure 4) (Xu et al., 2012). The transfer of proteins between the ER and LDs through their contact sites is regulated. The Arf1/COPI complex is well known for its function in vesicle trafficking between the ER and Golgi. Interestingly, Arf1/COPI proteins in *Drosophila* S2 cells are required for LD targeting of TAG synthesis enzymes, including DGAT2 and GPAT4. In addition to its Golgi localization, Arf1/COPI complex is localized on LDs, where it promotes the budding of nano-LDs from large LDs and the formation of ER-LD contact sites, two seemly unrelated events. The budding of nano-LDs appears to change the phospholipid composition of LDs and leads to the formation of ER-LD membrane bridges, supporting rapid protein transfer from the ER to LDs. This is supported by the protein targeting defects in Arf1/COPI-depleted cells being rescued by experimental manipulation of the LD membrane composition (Wilfling et al., 2014).

The ER to LD protein targeting pathway was recently defined further (Olarte et al., 2020; Song et al., 2022). This pathway can be separated into two phases: early ER-to-LD targeting and late ER-to-LD targeting. The former happens during LD biogenesis via the continuous membrane leaflet, and the latter is at mature LDs through the formation of ER-LD membrane bridges. The formation of ER-LD bridges requires certain tether proteins and SNAREs, including COG complex, Trs20, Bet1, and Syx5, as well as ERES proteins (Song et al., 2022).

## Protein functions

Several types of proteins are involved in ER-LD contacts. One type of protein is located in a subdomain of the ER, particularly the sites of LD biogenesis or in close proximity to LD biogenesis sites. Another type of protein is located on the LDs and binds with ER proteins to form ER-LD tethers.

Seipin is a "star" molecule in LD biogenesis. Seipin forms lipid-binding oligomers and labels the sites of LD biogenesis (Sui et al., 2018; Wang et al., 2016; Yan et al., 2018). Yeast mutants of *fld1*, the yeast homolog of mammalian *Seipin*, have both supersized LD and aggregated LD phenotypes (Fei et al., 2008; Szymanski et al., 2007). Fld and its binding protein Ldb16 are found at the ER-LD contact sites. In *fld1* and *ldb16* mutants, the ER-LD contact sites are distorted under the electron microscope; the uniform ER lumen is replaced with local luminal expansion. The electron density of the expanded ER lumen is similar to the core of LDs, which suggests that neutral lipids accumulate in the expanded region. In addition, the aggregated LDs frequently exhibit a wrinkled appearance and are often separated from the ER. The membrane defects of LDs are also evidenced by the aberrant localization of amphipathic helix-containing proteins, which mark membranes with lipid-packing defects (Grippa et al., 2015). Aberrant ER-LD contact sites and ER morphology have also been observed in human *Seipin* mutant cells. In addition, the trafficking of proteins and lipids from the ER to mature LDs, but not nascent LDs, is compromised in mutant cells (Salo et al., 2016). Therefore, in addition to their role in LD biogenesis, Seipin and its partners are also required for the morphology and function of ER-LD contact sites (Figure 4).

MDM1, a yeast membrane tether in the ER, is localized at the nucleus-vacuole junction for LD biogenesis during nutrient stress (Hariri et al., 2019). Sorting nexin 14 (Snx14), the mammalian homolog of MDM1, localizes at ER-LD contact sites in human U2OS cells upon oleic acid treatment. Snx14 promotes LD biogenesis by coordinating the action of ACSL3, a fatty acyl-CoA ligase, for the activation of fatty acids. Interestingly, overexpression of Snx14 increases ER-LD contact, whereas Snx14 knockout reduces the contact. In addition to ER-anchored transmembrane domains, Snx14 possesses an LD-binding amphipathic helix region at its C-terminus. Mechanistically, Snx14 uses this dual binding ability to tether the ER to LDs (Datta et al., 2019).

Rab18 is a conserved small GTPase localized at the ER and LDs. The reversible localization of Rab18 on LDs is regulated by its GAP and GEF. Once activated by GEF, GTP-bound Rab18 localizes to LDs, leading to its binding the ER tethering complex NRZ and its associated SNAREs. Formation of the Rab18-NRZ-SNARE complex promotes ER-LD contacts. Compared with control 3T3-L1 preadipocytes, loss of Rab18 causes fewer but larger LDs. Rab18 overexpression results in more ER-LD contact sites, whereas Rab18 deficiency reduces the number of ER-LD contact sites (Xu et al., 2018) (Figure 4). Double FYVE-containing protein 1 (DFCP1) is a Rab18 effector that contains an ER-targeting domain and two lipid-binding FYVE domains. Upon LD induction, DFCP1 localizes to LDs. The ER-targeting domain is essential for this localization. DFCP1 overexpression enhances ER-LD contact in cultured mammalian cells. Mechanistically, DFCP1 interacts with GTP-bound Rab18 to mediate ER-LD contact formation (Gao et al., 2019a; Xu et al., 2018).

In yeast, an ER-localized multi-transmembrane protein, Ice2p, localizes in the proximity of LDs when the cells transit from the stationary phase to the exponential growth phase. Loss of Ice2p delays TAG breakdown and locks yeast cells in a futile cycle in which TAG is broken down to diacylglycerol (DAG) and then re-synthesized from DAG. In wild-type cells, Ice2p may channel DAG from LDs to the ER upon TAG breakdown, facilitating the usage of DAG to generate membrane lipids (Markgraf et al., 2014). Vps13A and Vps13C are two Vps13 family proteins that are mutated in human neurodevelopmental and neurodegenerative disorders. Vps13A and Vps13C both possess two lipid-binding domains that facilitate their localization at MCSs between the ER and other organelles. A FFAT motif tethers them to the ER, and $DH_L$-PH domains at the C-terminal region target them to the LDs. In addition, the N-terminus of Vps13 exhibits lipid transfer activity. Therefore, Vps13A and Vps13C may transfer lipids between the ER and LDs (Kumar et al., 2018). CLSTN3β is a newly identified ER integral membrane protein and localizes at ER-LD contact sites upon LD induction. CLSTN3β associates with CIDE proteins and reduces the lipid transfer activity of CIDE proteins to prevent LD fusion and expansion (Qian et al., 2023).

### *Physiological significance*

ER-LD contact sites clearly contribute to cellular lipid homeostasis. Dysregulation of ER-LD contact caused by loss of function of the above proteins often leads to cellular lipid stress in the ER. Nevertheless, the physiological significance of ER-LD contact sites is still not fully understood. One reason for this is that ER-LD contact proteins are often multifunctional (Chung et al., 2015; Ding et al., 2018; Yeshaw et al., 2019), so when their function is lost, it is hard to determine the exact phenotypic contribution of the dysfunctional ER-LD contact. The intermingling of LD biogenesis and ER-LD contact formation is undoubtedly a relevant example. Seipin deficiency leads to complex phenotypes, including near complete absence of adipose tissue, dyslipidemia, hepatic steatosis, cardiomyopathy, and mental retardation (Magré et al., 2001). We cannot be sure whether such dramatic physiological consequences are due to defective LD biogenesis, dysregulated ER-LD contact sites, or both. Another reason is that loss of a single ER-LD tethering protein is unlikely to completely disrupt ER-LD contact sites. Usually, multiple pairs of tethering proteins act redundantly in maintaining organelle contacts. In addition, the biophysical properties of hydrophobic neutral lipids and amphipathic phospholipids support spontaneous LD biogenesis from the ER, which makes a complete absence of ER-LD contact unlikely. Therefore, the physiological consequences of ER-LD contact defects may be marginal in most scenarios. Other manipulations may be required to visualize the physiological significance of ER-LD contact sites.

## ER-autophagosome contact

Macroautophagy (hereafter autophagy) is a highly conserved eukaryotic catabolic process that sequesters aggregated proteins and excess/damaged organelles into double-membrane autophagosomes and delivers them to lysosomes for turnover (Feng et al., 2014; Gomez-Sanchez et al., 2021; Mizushima, 2018; Nakatogawa, 2020). This degradation pathway functions as an intracellular surveillance mechanism at the basal level, and also recycles surplus cytoplasmic components for cell survival during energy crisis. Malfunction of autophagy caused by genetic mutations or other factors, such as aging, is causally linked with various human pathologies, including neurodegenerative diseases, diabetes, cancer, inflammation, and immunological diseases (Zhao and Zhang, 2019). The ER plays an essential role in providing a platform, as well as a lipid source, for isolation membrane (IM) expansion into autophagosomes.

Autophagy occurs in a stepwise manner and requires multiple Atg proteins identified from yeast genetic screens. The core Atg proteins are divided into five subgroups (Figure 5): the Atg1/ULK1 kinase complex, VPS34 PI3P kinase complex, Atg2/ATG2s-Atg18/WIPIs (including WIPI1, WIPI2, WDR45 and WDR45B) complex, multiple transmembrane protein Atg9/ATG9, and the Atg12/ATG12 and Atg8/LC3 conjugation systems (Feng et al., 2014; Gomez-Sanchez et al., 2021; Mizushima, 2018; Nakatogawa, 2020). However, mammalian autophagy is far more complex than yeast autophagy, and genetic screens in multicellular model organism *C. elegans* discovered more metazoan-specific autophagy proteins, including EPG-3/VMP1, EPG-4/EI24, EPG5, and EPG-6/WDR45/45B, which are functionally conserved in mammals (Lu et al., 2011; Tian et al., 2010).

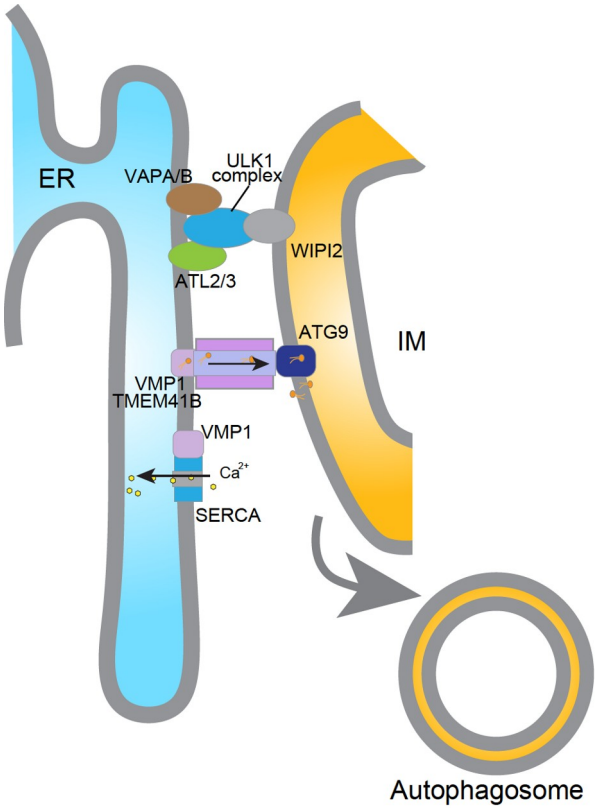



**Figure 5.** ER-autophagosome membrane contact sites and their functions. During autophagosome formation, the ER forms extensive contacts with the growing isolation membranes. IM-localized WIPI2 interacts with the ULK1/FIP200 complex and VAPA/B on the ER to mediate the ER-IM contacts. ATG2 also bridges the ER and IMs and mediates lipid transfer from the ER to IMs. VMP1/TMEM41B and ATG9 regulate the lipid balance between the phospholipid bilayers and collaborate with ATG2 for IM expansion through their scramblase activity on the ER and IMs, respectively. After the autophagosome is closed, VMP1 activates SERCA to dissociate the autophagosome from the ER, possibly by regulating local calcium levels.

The origin of membrane sources for the autophagosome and how they are formed are still unanswered questions. Although almost all intracellular organelles, including mitochondria, ER, endosomes, Golgi, and LDs, as well as the PM, have been reported to contribute to this process, a consensus is emerging that the ER plays an essential role during autophagosome biogenesis. In mammalian cells, the nucleation and further elongation of preautophagosomal structures, the IMs or phagophores, occur adjacent to ER subdomains (termed omegasomes) enriched in PI3P and labeled by DFCP1 (Axe et al., 2008). Ultrastructural analysis has also revealed that the ER closely apposes both sides of the autophagosomal membranes during IM expansion, forming sandwich-like structures (Hayashi-Nishino et al., 2009; Yla-Anttila et al., 2009). The ER and IMs also form direct connections via tubular membrane extensions (Hayashi-Nishino et al., 2009; Uemura et al., 2014; Yla-Anttila et al., 2009). Therefore, ER-IM contact is important for autophagosome formation, but the molecular mechanism underlying the establishment and disassociation of ER-IM contact sites and how the MCSs provide lipids for IM elongation are still under investigation.

After autophagy induction, the ULK1 and VPS34 complexes translocate to the ER adjacent to the autophagosome formation sites (Matsunaga et al., 2010; Nishimura et al., 2017), whereas

the ATG5-12 and LC3 conjugation systems are recruited to the growing IMs during autophagosome formation (Gomez-Sanchez et al., 2021; Nakatogawa, 2020). In mammalian cells, the ER-targeted ULK1 complex components ULK1 and FIP200 interact with IM-located WIPI2 to mediate ER-IM contact. Without WIPI2, DFCP1-labeled omegasomes are separable from LC3-positive autophagosomal structures. The autophagy-specific PI3P required for WIPI2 recruitment is also critical for establishing this contact (Zhao et al., 2017). VAP-A/B are tail-anchored ER proteins generally involved in ER contact with other membranes. Atlastin 2 and 3 (ATL2/3) belong to a family of ER spanning dynamin-like GTPases responsible for ER fusion. VAP-A/B and ATL2/3 function somewhat redundantly to recruit and stabilize the ULK1 complex on the ER, facilitating ER-IM contact formation (Liu et al., 2021; Zhao et al., 2018).

In yeast, the ERES has been shown to be a site where the extremities of the IM are tethered (Graef et al., 2013; Suzuki et al., 2013). The targeting of Atg2-Atg18 complex to the tip of the growing IMs, mediated by Atg9, builds up their contact with the ER. This tethering function of the Atg9-Atg2-Atg18 complex is essential for IM expansion (Gomez-Sanchez et al., 2018; Kotani et al., 2018). Recent *in vitro* liposome tethering assays revealed that mammalian ATG2, with the assistance of WDR45 at one end, bridges PI3P-containing vesicles with PI3P-free vesicles (Chowdhury et al., 2018). ATG2 tethers large unilamellar vesicles (LUVs) much less efficiently than small unilamellar vesicles (SUVs) (Maeda et al., 2019; Osawa et al., 2019). Given the diameter of autophagosomes (500–1,000 nm), this suggests that WIPIs are required for the tethering activity of ATG2 *in vivo*.

Distinct from the generation of other organelles, autophagosomes are formed through a *de novo* synthesis process requiring massive lipid mobilization. Both yeast Atg2 and mammalian ATG2s demonstrate lipid transfer activity, which is promoted by Atg18 and WIPIs, respectively (Maeda et al., 2019; Osawa et al., 2020; Osawa et al., 2019; Valverde et al., 2019). The autophagosomes are smaller in *Wdr45/45b* DKO cells, providing *in vivo* evidence for the role of the ATG2-WIPIs complex in delivering bulk glycerophospholipids from the ER to the IM for IM growth (Ji et al., 2021). Phospholipid synthesis by acyl-CoA synthetase Faa1 at the ER next to autophagosome formation sites also provides constant materials for IM growth (Schutter et al., 2020). Atg9, the sole transmembrane protein on autophagosomes, has been shown to be a lipid scramblase that transports lipids bidirectionally in the absence of ATP. This suggests that Atg9 translocates ER-derived phospholipids from the outer leaflet of the IM to the inner leaflet. Similarly, ER-localized VMP1 and its binding partner TMEM41B exhibit lipid scramblase activity *in vitro*, which suggests that they equilibrate lipids at the donor side (Ghanbarpour et al., 2021; Li et al., 2021b). As VMP1 also regulates the dissociation of closed autophagosomes from the ER, it plays a dual role during autophagosome biogenesis.

After IMs are closed into autophagosomes, they need to dissociate from the ER for subsequent maturation and degradation through fusion with endolysosomal compartments. The autophagy protein VMP1/EPG-3, a multi-spanning transmembrane ER protein, disassembles ER-IM contact sites by regulating ER-localized calcium transporter sarcoplasmic/ER $Ca^{2+}$ ATPase (SERCA). As the VPS34 kinase activity requires calcium and its effector CALM, SERCA activation may remove PI3P and disrupt IM contacts with the ER by decreasing the local calcium concentration at the autophagosome formation sites (Zhao et al., 2017). Loss of VMP1 also increases the ER contacts with other organelles, including LDs, endosomes, and mitochondria, which indicates a common role of the VMP1/SERCA pathway in the disassembly of ER contacts.

Although the lipid transfer activity of Atg2/ATG2 and scramblase activity of autophagosome-located Atg9/ATG9 and ER-docked VMP1/TMEM41B provide a promising mechanism for the transportation of phospholipid from the ER to IMs, *in vivo* evidence supporting this model is missing. Importantly, these activities are bidirectional in *in vitro* assays. Therefore, how the directionality of these processes is established needs further investigation. In addition, the function of the ULK1/FIP200/VAP-A/B-WIPI2 tether complex in ER-IM contact sites and whether it coordinates with the lipid transfer function of ATG2 is not known. Whether SERCA activity and/or local calcium regulate the lipid transfer process is another unanswered question. Further studies could disclose the mechanism of autophagy, but also provide insights into understanding the other organelles generated from or closely related to the ER.

## ER-PM contact

A tight association of the ER membrane with a small fraction of the PM was first reported in muscle cells with small gaps between them in 1957 using electron microscopy (Porter and Palade, 1957). Five years later, Rosenbluth described structures in neurons where the ER is apposed to a large fraction of the PM (Rosenbluth, 1962). These small "focal contacts" in muscles and large "subsurface cisternae" in neurons were subsequently shown to share similar features and called ER-PM junctions or ER-PM contact sites (Henkart et al., 1976). ER-PM contact sites are currently recognized as being present in almost all kinds of eukaryotic cells and are quantitatively and morphologically distinct among different cell types and cell states. In yeast, almost half of the PM is covered by the cortical ER (West et al., 2011). In most animal cells, the small ER-PM contact sites are frequently observed by electron microscopy with a distance of 10–30 nm, but they expand after the functional state of the cell changes, such as $Ca^{2+}$ store depletion (Fernandez-Busnadiego et al., 2015; Orci et al., 2009).

The biological significance of the ER-PM contact sites is based on studies identifying molecules at these sites that are vital for regulating $Ca^{2+}$ signaling and lipid metabolism in response to physiological stimuli. Much has been learned about the roles of ER-PM contact sites in $Ca^{2+}$ signaling events since the 1970s. One important milestone in this field was the discovery of store-operated $Ca^{2+}$ entry (SOCE), which is a required process for replenishing ER $Ca^{2+}$ stores and activating intracellular $Ca^{2+}$ -dependent signaling upon stimuli-induced ER $Ca^{2+}$ depletion (Hoth and Penner, 1992; Park et al., 2000; Penner et al., 1988; Putney, 1986; Putney, 1990). Another landmark study was the identification of ER membrane protein stromal interaction molecule 1 (STIM1), which interacts with PM $Ca^{2+}$ channel Orai1 to mediate SOCE (Feske et al., 2006; Liou et al., 2005; Roos et al., 2005; Vig et al., 2006; Zhang et al., 2006; Zhang et al., 2005). The involvement of ER-PM contact sites in lipid homeostasis has gained considerable attention over the past few years because a variety of proteins that function at these sites contain modules for non-vesicular lipid transport, including SMP domain (Bian and De Camilli, 2019; Lees et al., 2017; Qian et al., 2021; Saheki et al., 2016; Schauder et al., 2014; Yu et al., 2016), ORD

(Chung et al., 2015; Ghai et al., 2017; Maeda et al., 2013; Moser von Filseck et al., 2015a; Sohn et al., 2018; Stefan et al., 2011), StART and StART-like domains (Besprozvannaya et al., 2018; Gatta et al., 2015; Horenkamp et al., 2018; Jentsch et al., 2018; Laraia et al., 2019; Marek et al., 2020; Mesmin et al., 2011; Naito et al., 2019; Sandhu et al., 2018; Tong et al., 2018), and PITP domain (Chang et al., 2013; Cockcroft et al., 2016; Kim et al., 2013; Kim et al., 2015; Milligan et al., 1997).

## *Structure of ER-PM contact sites*

The identification of STIM genes and Orai genes paved the way for understanding the biogenesis and dynamics of ER-PM contact sites. STIM1 is an integral ER membrane protein and stays in an inactive form as a monomer or dimer. When the $Ca^{2+}$ level in the ER lumen decreases, the release of $Ca^{2+}$ from the combined EF-SAM-domain $Ca^{2+}$-binding sites at the N-terminus of STIM1 triggers its clustering (Stathopulos et al., 2009; Stathopulos et al., 2008). The STIM1 oligomer then interacts with and activates PM-localized Orai1 through its STIM1 Orai1 activation region (SOAR) domain to enlarge the ER-PM contact sites (Figure 6) (Kawasaki et al., 2009; Park et al., 2009; Yuan et al., 2009). Finally, restoration of the ER $Ca^{2+}$ level leads to the dissociation of STIM1 from ER-PM contact sites.

Several factors that regulate the STIM-Orai interaction have been identified. PI4P and $PI(4,5)P_2$, two phosphoinositides that are enriched in the PM, can interact with the C-terminal polybasic region of STIM1 to enhance its targeting to ER-PM contact sites (Korzeniowski et al., 2009; Liou et al., 2007; Nakatsu et al., 2012). In addition to lipids, STIM1-binding ER resident proteins, including $Ca^{2+}$-sensing EF-hand motif-containing protein junctate (Srikanth et al., 2012), MORN motif-containing protein junctophilin 4 (JPH4) (Woo et al., 2016), and polybasic-tail-containing protein TMEM110/STIMATE (Jing et al., 2015; Quintana et al., 2015), also facilitate ER-PM contact site recruitment of STIM1. In the case of Orai1, its diffusion restriction by septin 4 (Sharma et al., 2013) and stabilization by cytosolic $Ca^{2+}$-sensing EF-hand motif-containing protein CRACR2A (Srikanth et al., 2010) promote its assembly with STIM1. In contrast, the ER protein SARAF (Palty et al., 2012) and microtubule plus-end-tracking protein EB1 (Chang et al., 2018) inactivate the SOAR domain of STIM1 and restrict STIM1 at the plus ends of microtubules to prevent its translocation to ER-PM contact sites.

Although the STIM-Orai interaction plays an important role in ER-PM contact site formation, it is absent in yeast, in which ER-PM contact sites are abundant. This raises the possibility that additional mechanisms exist for ER-PM contact site biogenesis. A groundbreaking study by Emr's group identified three protein families that tether the ER to the PM in yeast: tricalbins (Tcbs), Scs2/22, and Ist2 (Manford et al., 2012). Tcbs and their homologs in animal cells, extended synaptotagmins (E-Syts), are anchored to the ER membrane via their N-terminal hydrophobic hairpin and use their C2 domains to bind to the PM (Figure 6). Three E-Syts are known in human cells: E-Syt1, E-Syt2, and E-Syt3 (Min et al., 2007). In contrast to E-Syt2 and E-Syt3, which are constitutive ER-PM tethering proteins, most E-Syt1 molecules are distributed throughout the entire tubular ER membrane at the resting cytosolic $Ca^{2+}$ level. $Ca^{2+}$ influx from the extracellular medium triggers the recruitment of E-Syt1 together with the ER membranes to the PM, which is further expanded by $Ca^{2+}$ release from the ER (Chang et al., 2013; Giordano et al., 2013; Idevall-Hagren et al., 2015; Xie et al., 2019). The mechanisms for E-Syts-mediated ER-PM tethering have been investigated using biological, biochemical, and biophysical methods. The binding of E-Syts to the PM relies on the interactions of polybasic patches in their C-terminal C2 domains (C2E in E-Syt1 and C2C in E-Syt2/3) with $PI(4,5)P_2$ in the PM. An additional mechanism for regulating the dynamic behavior of E-Syt1 was revealed by single-molecule experiments using optical tweezers, in which the affinity of its C2E domain for the membrane was too weak to be stably tethered to the PM despite having a strong similarity to the C2C domain of E-Syt2, and the $Ca^{2+}$-bound C2C domain of E-Syt1 provides additional membrane-binding force to stabilize the ER-PM contact sites (Ge et al., 2022).

Another ER-PM tether identified in yeast is Scs2/22. Though Scs2 is localized throughout the ER, its loss alone can cause a reduction in cortical ER (Manford et al., 2012). Scs2/22 and their homologs in mammals, VAPs, contain major sperm protein (MSP) domains followed by transmembrane segments, and there is a coiled-coil region between these two domains for dimerization in VAPs (Kaiser et al., 2005). The MSP domain has been suggested to interact with a number of FFAT motif-containing proteins, which bind the PM in trans, to establish ER-PM contact sites. Among the FFAT motif-containing proteins, oxysterol-binding homology (Osh) proteins in yeast and ORPs in mammals are well-studied. In mammals, ORP5 and ORP8 translocate to the PM depending on PI4P and $PI(4,5)P_2$. However, as they are integral ER membrane proteins, VAPs are not required for their localization (Figure 6) (Chung et al., 2015; Ghai et al., 2017; Sohn et al., 2018). Instead, two other ORPs, ORP3 and ORP6, are recruited by VAPs to ER-PM contact sites (Mochizuki et al., 2018). Interestingly, the PM-targeted ORP2 (Jansen et al., 2011) does not concentrate at MCSs even though it contains a FFAT motif (Wang et al., 2019). Another representative member of FFAT motif-containing proteins is retinal degeneration B (RdgB) in *Drosophila* (Nirs in mammals), which is targeted to E-Syt-mediated ER-PM contact sites upon phospholipase C (PLC)-induced DAG and PA generation (Figure 6) (Chang et al., 2013; Chang and Liou, 2015; Kim et al., 2015; Nath et al., 2020; Quintanilla et al., 2022; Saheki et al., 2016; Yadav et al., 2016). In addition to cytosolic proteins, VAPs also recruit PM proteins. For example, the clustered Kv2 potassium channel interacts with VAPs at ER-PM contact sites in resting neurons (Figure 6). In response to neuronal stimuli, the VAPs dissociate from Kv2 in a $Ca^{2+}$- and calcineurin-dependent manner (Fox et al., 2015; Johnson et al., 2018; Kirmiz et al., 2018).

Quantitative proteomic analysis in yeast has identified Ist2, which accumulates at ER-PM contact sites (Manford et al., 2012). The ER-anchoring of Ist2 occurs via its eight transmembrane domains, and its binding to $PI(4,5)P_2$ and other lipids in the PM is mediated by its C-terminal polybasic stretch (Fischer et al., 2009). In mammals, there is sequence similarity between Ist2 and the $Ca^{2+}$-activated $Cl^-$ channel and/or lipid scramblase TMEM16/anoctamin (ANO) protein family. However, no strong evidence is available for targeting most members of this family to ER-PM contact sites. Only ANO8 was recently shown to translocate to $PI(4,5)P_2$-enriched STIM-Orai interaction-mediated contact sites upon $Ca^{2+}$ store depletion (Figure 6) (Jha et al., 2019).

The list of ER-PM tether proteins has grown rapidly in recent

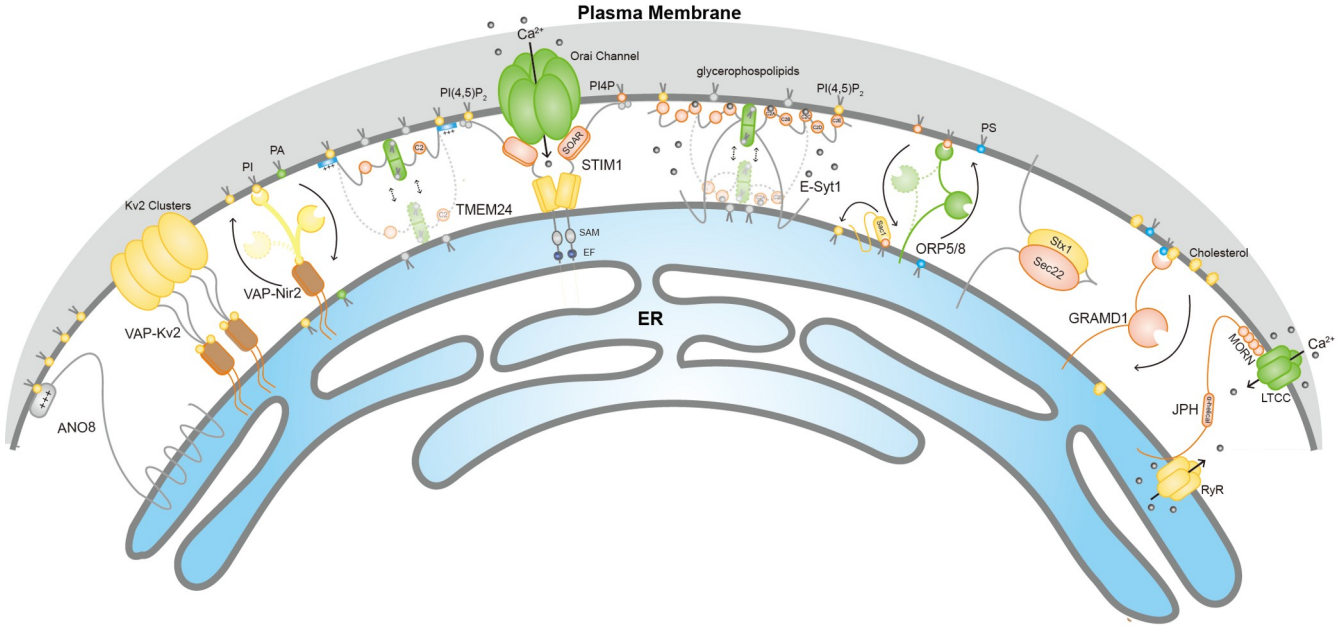



**Figure 6.** Examples of proteins that mediate ER-PM contacts and function at these sites in mammals. Upon ER $Ca^{2+}$ store depletion, STIM1 oligomer interacts with and opens the PM $Ca^{2+}$ channel Orai1 to mediate SOCE. $Ca^{2+}$ binding to E-Syt1 releases its autoinhibitory state to couple ER-PM tethering with lipid transport to regulate PM lipid homeostasis in response to stimuli. The ER membrane proteins ORP5/8 bind to the PM, depending on PI4P and $PI(4,5)P_2$, and transport PI4P, which is dephosphorylated by Sac1 in the ER to generate PI and provide energy for transporting PS from the ER to the PM by the same proteins. The VAP-interacting protein Nir2, which is translocated to ER-PM contact sites by DAG and PA generated by $PI(4,5)P_2$ hydrolysis, exchanges PI and PA to couple $PI(4,5)P_2$ resynthesis with its consumption. The clustered Kv2 channel interacts with VAP at ER-PM contact sites in resting neurons with a potential role in coupling lipid metabolism and Kv2 channel function. The ER protein ANO8, with eight transmembrane domains, binds to $PI(4,5)P_2$ in the PM to prevent excessive $Ca^{2+}$ influx and cell toxicity. At resting cytosolic $Ca^{2+}$ levels, TMEM24 interacts with the PM through its C-terminal region to transport lipids, which facilitates glucose-induced insulin secretion in pancreatic β cells. ER R-SNARE Sec22 and PM Q-SNARE Stx1 form a non-fusogenic SNARE complex that contributes to PM expansion. ER-anchored JPHs, which bind to ryanodine receptors in the ER and interact with acidic phospholipid and $Ca^{2+}$ channel in the PM, facilitate $Ca^{2+}$ release from the ER and $Ca^{2+}$ influx from the PM to regulate excitability in muscles and neurons. ER-localized GramD1b is recruited to ER-PM contact sites by accessible cholesterol and PS in the PM and transports cholesterol from the PM to the ER.

years. TMEM24/C2CD2L is an SMP domain-containing ER resident protein enriched in pancreatic β-cells and neurons. At rest, it populates ER-PM contact sites via its basic C-terminal region, which is phosphorylated by PKC in response to an increase in cytosolic $Ca^{2+}$, dissociating the protein from the PM (Figure 6) (Lees et al., 2017; Sun et al., 2019). Another important ER-PM tether in neurons is made up of ER R-SNARE Sec22 and PM Q-SNARE syntaxin 1 (Stx1). They can form a *trans*-SNARE complex to bridge the ER to the PM without mediating membrane fusion (Figure 6) (Petkovic et al., 2014). In muscles and neurons, JPHs are ER-anchored proteins and use their MORN motifs to interact with acidic phospholipids in the PM (Landstrom et al., 2014; Takeshima et al., 2000). They also bind RyRs in the ER and the L-type voltage-gated $Ca^{2+}$ channel, NMDA receptors, or small conductance $Ca^{2+}$-activated $K^+$ channels in the PM (Figure 6) (Golini et al., 2011; Holmes et al., 2001; Moriguchi et al., 2006). Cholesterol is another kind of lipid that is enriched in the PM. When the PM cholesterol level increases, it can be detected by the GRAM domains of StART-like domain-containing ER proteins GRAMD1s/Asters (Lam/Ltc proteins in yeast that are constitutive ER-PM tethering proteins), which also interact with anionic lipids with distinct recognition sites in the GRAM domains or after the StART-like domain to form ER-PM contact sites (Figure 6) (Besprozvannaya et al., 2018; Ercan et al., 2021; Ferrari et al., 2020; Gatta et al., 2015; Marek et al., 2020; Naito et al., 2019; Sandhu et al., 2018; Tong et al., 2018). Electron cryo-tomography (cryo-ET) and super-resolution microscopy have been used to further observe the architectures of ER-PM contact sites by different tethers. For example, expressing ORP5 in mammalian cells or Scs2 and Ist2 in yeast leads to sheet-like ER membranes apposed to the PM, whereas E-Syts/Tcbs induces highly curved tubular ER membranes or ring-like structures at ER-PM contact sites (Collado et al., 2019; Hoffmann et al., 2019; Kang et al., 2019; Zhang et al., 2020b).

## *Physiological importance*

ER-PM contact sites gained interest after they were first observed in muscles and neurons. In muscle cells, the opening of clustered RyRs for $Ca^{2+}$ release from the ER is essential for regulating actomyosin remodeling, leading to muscle contraction (Endo, 2009; Landstrom et al., 2014; Schneider and Chandler, 1973). This process occurs at ER-PM contact sites and is triggered by clustered L-type voltage-gated $Ca^{2+}$ channels upon PM depolarization and assisted by JPH1/2. A similar $Ca^{2+}$-based mechanism for neuronal excitability has also been reported, in which RyRs, JPH3/4 in the ER, and NMDA receptors or small conductance $Ca^{2+}$-activated $K^+$ channels in the PM are required. The significant roles of ER-PM contact sites in this process are indicated by triplet repeats of the JPH3 gene leading to a neurodegenerative disease called HDL2 and JPH3/4 double-knockout mice exhibiting a defect in hippocampal plasticity (Holmes et al., 2001; Moriguchi et al., 2006). Interestingly, the roles of ER-PM contact sites in actomyosin regulation have been extensively studied in fission yeast *Schizosaccharomyces pombe*, in


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which these MCSs influence actomyosin structures through steric effects. The anillin-like Mid1 protein activates actomyosin components, forming cytokinetic "nodes" at the equatorial PM during mitotic entry (Zhang et al., 2016; Zhang et al., 2010). The cortical ER pattern and abundance determine regions of accessible PM for initial ring allocation (Zhang et al., 2016; Zhang et al., 2010; Zhang et al., 2012). Scs2/Scs22-mediated ER-PM contact sites restrict adjacent node mobility during ring compaction, which is essential for proper ring assembly (Zhang et al., 2016).

In addition to controlling excitability in muscles and neurons, ER-PM contact sites also play important roles in regulating $Ca^{2+}$ signaling events in all cell types. In response to physiological stimuli, the second messenger $IP_3$, which is generated by PLC-hydrolyzed PI(4,5)$P_2$, activates $IP_3$-receptor to release $Ca^{2+}$ from the ER for signaling functions involved in cell physiology (Berridge and Irvine, 1989). The STIM1 oligomer induced by ER $Ca^{2+}$ loss binds to and opens the Orai1 channel at ER-PM contact sites for $Ca^{2+}$ influx ($Ca^{2+}$ release-activated channels, CRACs) to slowly refill ER $Ca^{2+}$ stores through SERCA pumps in the ER membrane and generate additional cytosolic $Ca^{2+}$ signals (Figure 6). This process, SOCE, is inactivated by ANO8, which translocates to STIM-Orai interaction-mediated contacts and recruits SERCA2 for rapid replenishment of ER $Ca^{2+}$ stores to prevent excessive $Ca^{2+}$ influx and cell toxicity (Jha et al., 2019). Loss-of-function mutations in STIM1 and Orai1 lead to severe combined immunodeficiency (SCID)-like disease, autoimmunity, ectodermal dysplasia, and muscular hypotonia, whereas gain-of-function mutations in these two proteins that constitutively activate CRAC cause Stormorken syndrome, York platelet syndrome, and tubular aggregate myopathy (TAM) (Feske et al., 2006; Lacruz and Feske, 2015; Picard et al., 2009).

ER-PM contact sites also play fundamental roles in regulating the balance between phospholipids, sphingolipids, and sterols (Quon et al., 2018). After PI(4,5)$P_2$ is hydrolyzed by PLC to generate second messengers DAG and $IP_3$, it needs to be rapidly resynthesized because a variety of proteins directly bind to PI(4,5)$P_2$ to regulate many important cellular processes, including endocytosis, exocytosis, cytokinesis, and viral budding, among others. Though the lipid kinases-mediated phosphorylation for generating PI4P, PI(4,5)$P_2$, and PI(3,4,5)$P_3$ occurs in the PM, their precursor PI is synthesized in the ER. Thus, non-vesicular lipid transport at ER-PM contact sites is critical for this phosphoinositide cycle. Among PITP, the VAP-binding protein Nir2 is responsible for the transport of PI from the PM to the ER. PA, which is produced by DAG kinases upon DAG generation, is also transported by Nir2 from the PM to the ER to be converted to PI (Figure 6) (Chang et al., 2013; Kim et al., 2013; Kim et al., 2015). The PI/PA exchange capacity of Nir2 couples PI(4,5)$P_2$ resynthesis with its consumption.

The SMP domain is a newly identified non-vesicular lipid transfer module (Figure 6) (AhYoung et al., 2015; Alva and Lupas, 2016; Jeyasimman and Saheki, 2020; Kopec et al., 2010; Kornmann et al., 2009; Lee and Hong, 2006; Lees et al., 2017; Reinisch and De Camilli, 2016; Saheki et al., 2016; Schauder et al., 2014; Toulmay and Prinz, 2012; Wong et al., 2019; Wong and Levine, 2017; Yu et al., 2016). Though the possibility of a tunnel mechanism for the SMP dimer cannot be ruled out, *in vitro* observations confirm that it can act as a shuttle to transport lipids between tethered bilayers (Bian et al., 2019; Wang et al., 2023). The SMP domain-containing protein TMEM24 has been shown to transport PI from the ER to the PM to replenish PI(4,5)$P_2$ pools, which is required to sustain the glucose-induced $Ca^{2+}$ oscillations and insulin secretion in insulin-secreting cells (Lees et al., 2017; Pottekat et al., 2013; Xie et al., 2022). During the phosphoinositide cycle, the lipid second messenger DAG needs to be rapidly removed from the PM. Two pathways for DAG clearance have been reported: one is to be phosphorylated to PA, and the other is to be transported by another SMP domain-containing protein, E-Syts, to the ER. Knockout or knockdown of E-Syts causes prolonged accumulation of DAG in the PM, which amplifies glucose-stimulated insulin secretion (Saheki et al., 2016; Xie et al., 2019). In RdgB-mutant *Drosophila*, loss of E-Syt slows the PI(4,5)$P_2$ resynthesis rate in the photoreceptor PM, resulting in enhanced retinal degeneration (Nath et al., 2020). However, mice lacking all three E-Syts are viable and have no defect in development and propagation, which may be compensated by enhanced expression of other ER-PM tethers and lipid transfer proteins (Sclip et al., 2016; Tremblay and Moss, 2016). Phenotypes of E-Syt-null mice under specific conditions require further investigation. Interestingly, ablation of *E-Syt3* in mice has been shown to protect against diet-induced obesity and comorbidities (Zhang et al., 2020a).

ORD has been reported to harbor and transport phospholipids and sterols between artificial liposomes *in vitro* (Antonny et al., 2018; Dong et al., 2019; Manik et al., 2017; Mesmin et al., 2013; Moser von Filseck et al., 2015b; Raychaudhuri et al., 2006; Schulz et al., 2009; Tian et al., 2018; Wang et al., 2019). The ER-PM tethering protein ORP5/8 is designed to control PI4P and PI(4,5)$P_2$ levels by transporting them to the ER, where PI4P is dephosphorylated by Sac1. The PI4P gradients between the PM and ER drive the counter-transport of PS by the same proteins (Figure 6) (Chung et al., 2015; Ghai et al., 2017; Sohn et al., 2018). For sterol transport, Osh2 in yeast has been shown to deliver it from the ER to the PM through its ORD to trigger actin polymerization for endocytosis (Encinar Del Dedo et al., 2021). However, strong evidence is lacking for the roles of other Osh proteins involved in direct regulation of the PM ergosterol level. In mammals, ORP1S and ORP2 influence PM cholesterol homeostasis, but their transport of sterol from the PM to the ER at MCSs has been challenged (Wang et al., 2019; Zhao et al., 2020).

As the majority of Osh/ORPs have not been shown to mediate non-vesicular sterol transport between the ER and PM, other lipid transfer proteins are likely implicated in this process. StART and StART-like domains are sterol transfer modules (Alpy and Tomasetto, 2014; Clark, 2012; Ercan et al., 2021; Gatta et al., 2015; Horenkamp et al., 2018; Jentsch et al., 2018; Laraia et al., 2019; Naito et al., 2019; Rodriguez-Agudo et al., 2019; Sandhu et al., 2018; Stocco, 2001; Wilhelm et al., 2017). Yeast lacking StART-like domain-containing and ER-PM contact-localized proteins Ysp1/Lam1, Sip3/Lam3, Ysp2/Lam2/Ltc4, or Lam6/Ltc1 exhibit accumulation of sterol in the PM, causing increased sensitivity to antifungal drug Amphotericin B (Gatta et al., 2015; Marek et al., 2020). Consistent with this, the accumulated cholesterol in the PM of mammalian cells due to LDL-derived NPC1/2-dependent delivery or SR-BI-mediated HDL uptake is transported to the ER by GRAMD1s/Asters via their StART-like domains at ER-PM contact sites (Figure 6) (Gatta et al., 2015; Hoglinger et al., 2019; Naito et al., 2019; Sandhu et al., 2018; Trinh et al., 2020; Xiao et al., 2021). GRAMD1B/Aster-B knockout zebrafish have reduced brain activity, and depletion

of these proteins in mice results in defects in adrenal cholesterol ester storage and steroidogenesis (Sandhu et al., 2018; Thyme et al., 2019). Among 15 StART domain proteins in mammals, STARD4 facilitates the delivery of sterol between the PM and other organelles, including the ER and recycling endosomes (Iaea et al., 2017; Iaea et al., 2020; Mesmin et al., 2011; Rodriguez-Agudo et al., 2011; Rodriguez-Agudo et al., 2019), despite loss of STARD4 not affecting mouse viability and cholesterol metabolism (Riegelhaupt et al., 2010). Thus, sterol transfer proteins in mammals likely have redundant functions.

Interestingly, some ER-PM tethers may also mediate contacts between the ER and other intracellular organelles, which may represent general features of MCSs (Du et al., 2020; Galmes et al., 2016; Xiao et al., 2019). The identification of lipid cargoes by lipid transfer proteins and establishing protein-protein interaction networks at ER-PM contact sites remain fundamental areas of study. The application of advanced techniques, including cryo-ET, super-resolution microscopy, optical tweezers, DNA origami, and development of lipid probes, will aid in discovering new structures and functions of ER-PM contact sites.

## Conclusions and perspectives

ER-involved MCSs have been studied extensively, but additional mechanisms, regulation, and functions are yet to be investigated. New tools for contact analysis and systematic probing of contact-based physiology in various contexts are urgently needed. Weak interactions between the ER and other organelles are challenging to characterize but appear to have undetermined importance. ER morphology has been thought to be largely dependent on the cytoskeleton (Terasaki et al., 1986; Waterman-Storer and Salmon, 1998), but recent studies have revealed that the ER exerts significant influence on the cytoskeleton (Liu et al., 2019a; Farias et al., 2019; Zheng et al., 2022; Tikhomirova et al., 2022). Thus, the ER may serve as a new form of "skeleton" for many organelles by establishing contact sites with them.

### Compliance and ethics

The author(s) declare that they have no conflict of interest.


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