Review

Sigma 1 Receptor, Cholesterol and Endoplasmic Reticulum Contact Sites

Contact
Volume 4: 1–7

DOI: 10.1177/2515256421026505
journals.sagepub.com/home/ctc
SAGE

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Abstract

Recent studies indicated potential importance of membrane contact sites (MCS) between the endoplasmic reticulum (ER) and other cellular organelles. These MCS have unique protein and lipid composition and serve as hubs for inter-organelle communication and signaling. Despite extensive investigation of MCS protein composition and functional roles, little is known about the process of MCS formation. In this perspective, we propose a hypothesis that MCS are formed not as a result of random interactions between membranes of ER and other organelles but on the basis of pre-existing cholesterol-enriched ER microdomains.

Keywords

endoplasmic reticulum, membrane contact sites, mitochondria-associated membranes, cholesterol, lipid microdomains, sigma-1 receptor

Spatial Organization of the Endoplasmic Reticulum and Membrane Contact Sites

The endoplasmic reticulum (ER) is the largest cellular organelle. The total area of the ER membrane exceeds the area of the plasma membrane (PM) by ten to twenty times (Voeltz et al., 2002; Csordas et al., 2018). ER provides lipids, transmembrane and secreted proteins for many cellular processes, and also serves as a main store for intracellular Ca^{2+} (Phillips and Voeltz, 2016). ER membrane was initially considered to be uniform, but more recently it became clear that ER membrane is organized into sub-compartments where specific signaling and macromolecule transfer processes take place (Voeltz et al., 2002; Phillips and Voeltz, 2016; Zhang and Hu, 2016; Joshi et al., 2017; Cohen et al., 2018). Examples of such ER compartmentalization include membrane contact sites (MCS) formed between the ER and other organelles such as mitochondria, plasma membrane, lysosomes, endosomes, and lipid droplets (Carrasco and Meyer, 2011; Vance, 2014; Raiborg et al., 2015; Chang et al., 2017; Henne, 2017; Csordas et al., 2018; Henne, 2019). Other specialized areas of ER membrane include ER exit sites (ERES) (Kurokawa and Nakano, 2019), sites of ER-associated protein degradation (ERAD) (Albert et al., 2020), sites of autophagosome formation (Hayashi-Nishino et al., 2009), sites of organelle biogenesis (Joshi et al., 2017) and an ER quality compartment (Shenkman and Lederkremer, 2019). In the recent years, membrane contactology, or the cell biology of MCS, has attracted significant attention (Voeltz et al., 2002; Csordas et al., 2018).

MCS are defined as relatively stable (over the course of at least a few minutes, usually much longer) (Friedman et al., 2010) and small (submicron scale) areas where two organelle membranes are located in close proximity of each other (Scorrano et al., 2019). The function and composition of many MCS have been comprehensively described in recent reviews (Phillips and Voeltz, 2016; Csordas et al., 2018; Scorrano et al., 2019). ER MCS are stabilized by molecular interactions between protein tethers – proteins that form a physical linkage between ER membrane and the

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Received May 21, 2021. Revised June 1, 2021. Accepted June 1, 2021.

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membrane of a partner organelle. Tethering can be also mediated by interactions of ER proteins with lipids on a partner membrane (Prinz et al., 2020).

Among the best studied examples of MCS are mitochondria associated membranes (MAMs) (Csordas et al., 2018; Vance, 2020). MAMs are defined as regions of the ER in close proximity to mitochondria. MAMs play important roles in mediating inter-organelle communication, including lipid transfer between the organelles (Vance, 2020), ER-to-mitochondria Ca^{2+} signaling (Hajnoczky et al., 2002; Csordas et al., 2018), ATP production (Hajnoczky et al., 2002), autophagosome formation (Garofalo et al., 2016), ER stress response (van Vliet and Agostinis, 2018) and many other functions. Importantly, these functions of MAMs are dysregulated in several metabolic conditions, neurological disorders and cancers (Sano et al., 2009; Schon and Area-Gomez, 2013; Annunziata et al., 2018; Morciano et al., 2018). ERMES protein complex was demonstrated to play a key role in MAM maintenance in yeast cells (Kornmann et al., 2009). Stabilization of MAMs in eukaryotic cells appears to be a much more complex process that involves multiple redundant protein complexes. As many as several hundred of proteins have been demonstrated to be enriched at MAMs, many of them directly and indirectly affecting stability of MAMs as well as their function (Poston et al., 2013; Hung et al., 2017; Wang et al., 2018; Cho et al., 2020).

A Hypothesis Regarding Endoplasmic Reticulum Membrane Contact Site Formation

Despite extensive research on the molecular composition of MCS and MAMs in particular, very little is known about initial stages of MCS formation in cells. It was proposed that apart from direct protein tethering, several factors may play a role in formation and stabilization of MCS. For example, it was shown that association of ER and mitochondria with acetylated microtubules restricts the mobility of the organelles, thus favoring their docking to each other (Friedman et al., 2010). Fast Ca^{2+} release from the ER reduces mitochondrial motility and thus may promote association between the ER and mitochondria at the sites of Ca^{2+} signaling nanodomains (Yi et al., 2004; Saotome et al., 2008; Wang and Schwarz, 2009). Exogenously and endogenously generated reactive oxygen species also play a role in restrickting the mitochondrial motility, potentially helping them to dock to the ER (Debattisti et al., 2017).

Since tethers are ubiquitously present on the membranes of two organelles, one possibility is that ER membrane comes in contact with mitochondria and other partner organelles in a stochastic manner, consistent with the "stochastic encounter model" (Figure 1A). In this scenario, contact sites can be formed at any part of the ER membrane. After formation of initial contacts, further MCS maturation could be achieved by recruiting more tethers and by remodeling of the local lipid composition of the ER membrane, eventually resulting in stable mature MCS (Figure 1A).

We would like to propose an alternative "microdomain-directed model" (Figure 1B). Specifically, we would like to propose that MCS formed not randomly but on the basis of pre-existing cholesterol-enriched microdomains in the ER membrane. Our recent in vitro reconstitution and cell biological studies indicated that ER resident protein sigma-1 receptor (S1R) is able to self-assemble in the membranes in a manner dependent on cholesterol (Zhemkov et al., 2021a). We have also observed that proteins with longer transmembrane domains were recruited to these clusters (Zhemkov et al., 2021a), leading us to a conclusion that S1R can help to organize thick and cholesterol-rich microdomains in the ER membrane (Zhemkov et al., 2021a,b). It is plausible that MCS tethers are concentrated in these microdomains due to a preference of these proteins for thicker membrane and/or cholesterol (Figure 1B). It has been shown that local ER membrane thickness depends on cholesterol levels and is influenced by the density of transmembrane proteins (Mitra et al., 2004). One of the candidates for such a role is inositol 1,4,5-trisphosphate receptor ($InsP_3R$). It is known that $InsP_3R$ serves as an MCS tether in MAMs via association with glucose-regulated protein 75 (grp75) and voltage-dependent anion channel (VDAC) in the mitochondrial outer membrane (Szabadkai et al., 2006). $InsP_3Rs$, specifically $InsP_3R$ type 3, are also known to be enriched in MAM and colocalize with S1R (Hayashi and Su, 2007). S1R increases stability of the $InsP_3R$ under resting conditions and activates $InsP_3$-induced Ca2+ release upon ligand activation (Hayashi and Su, 2001; 2007; Watanabe et al., 2016). Other known MCS tethers (such as MFN2, VAPB, BAP31, PDZD8 in case of MAMs (Reane et al., 2020)) may also be enriched in these microdomains. Several detergent-resistant membrane-targeting mechanisms have been described, including protein palmitoylation (TMX, calnexin and APP) (Lynes et al., 2012; Bhattacharyya et al., 2013, 2021), and the presence of certain protein domains such as prohibitin-domain in erlins (Browman et al., 2006). Transmembrane domain length and sequence features determine raft localization of plasma membrane proteins (Lorent et al., 2017) and similar targeting mechanisms may exist for ER resident proteins. We further propose that when these rigid cholesterol-rich and flat microdomains come in contact with mitochondria and other organelles, stable contacts can be readily formed (Figure 1B). Once initial contact is formed, it can be further stabilized and expanded as

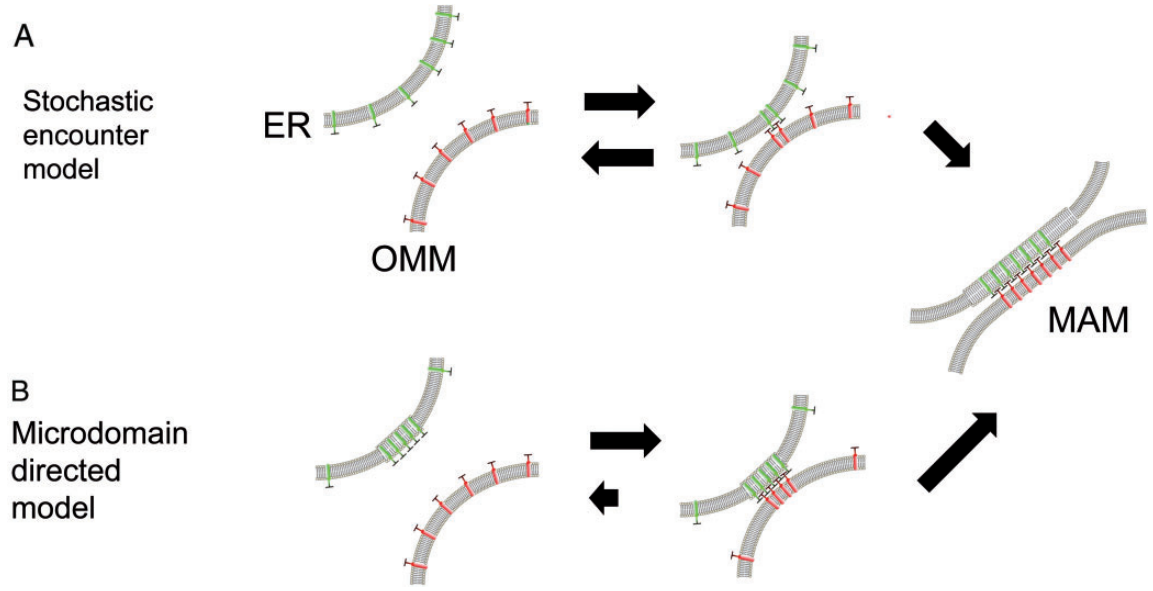

Figure 1. Alternative Models of Endoplasmic Reticulum Membrane Contact Site Formation. An example of ER-mitochondria (MAM) contact site formation. Protein tethers are present on the ER membrane (green Ts) and the outer mitochondria membrane (red Ts) (left panels). When ER and mitochondria membranes come into proximity with each other, a transient MCS intermediate is formed (middle panels). These MCS intermediates may disintegrate or convert to mature MCS (right panel). Two potential models of MCS formation are considered. A: Stochastic encounter model. Protein tethering molecules uniformly distributed in the ER membrane and in the membranes of the partner organelles (outer mitochondria membrane in this example). Molecular interactions between ER and mitochondrial tethers occur randomly due to stochastic movements of the membranes. When sufficient numbers of tethers from two organelles interact with each other at the same location by chance, contact sites become stabilized and formation of the stable MCS is achieved by recruitment of additional proteins and/or through remodeling of the local ER membrane lipid composition. B: Microdomain-directed model. Specialized lipid microdomains pre-exist in the ER membrane, such as those stabilized by sigma-1 receptor (S1R). These microdomains are characterized by higher cholesterol content, increased bilayer thickness and flat geometry (marked as thick lipid patches on the ER membrane). MCS ER protein tethers are postulated to be enriched in these microdomains. When these microdomains come into proximity with the partner organelle membrane (outer mitochondria membrane in this example), they are immediately able to form relatively stable initial contacts. These initial contacts mature to become MCS by recruitment of additional tethers, signaling proteins and lipids.

a result of MCS maturation (Csordas et al., 2010) (Figure 1B).

The proposed model depicted on Figure 1B is consistent with biochemical studies that suggested that MAMs are enriched in cholesterol and ceramides (Hayashi and Fujimoto, 2010; Area-Gomez et al., 2012; Montesinos et al., 2020; Anastasia et al., 2021). A recent in-depth cryo-electron microscopy, proteomic and lipidomic study of rough ER-mitochondria contact areas in liver hepatocytes showed that these areas are enriched in cholesteryl esters, sphingomyelins and serve as sites for the secretion of very low density lipoproteins (Anastasia et al., 2021). Certain MCS show membrane phase separation when probed with a liquid-order localized membrane reporter (King et al., 2020). Liquid-ordered membrane domains were observed for ER-mitochondria, ER-PM, and ER-lipid droplet contact sites (King et al., 2020). Recently, it was observed that in phosphatidylserine-deficient yeast strain, a large sterol-rich 'void' zone can be formed on the PM (Mioka et al., 2022). Vacuole-PM MCS is preferentially formed with the void zone, even though it is depleted of integral and peripheric membrane proteins (Mioka et al., 2022). According to the proposed model, it is likely that the unique lipid composition of the ER membrane at the MCS is a direct consequence of unique lipid composition of pre-existing ER microdomains that formed the initial basis for their formation.

It is also important to point out that proposed mechanism may not universally apply to all cells and all contact sites. For example, in budding yeast ER-PM MCS dramatically increased in response to sterol depletion, suggesting that other mechanisms may be in play in this case (Quon et al., 2018). Also, topology of the contacts between the ER and endo/lysosomes in mammalian cells requires curved membrane and flat and rigid S1R microdomains may preclude such contacts from forming. Therefore, these contacts are more likely to form by flexible ER membrane outside of rigid S1R microdomains.

Conclusions

We propose a new hypothesis that S1R-formed cholesterol-enriched ER microdomains form a basis for the initial formation of MCS between the ER and other

organelles such as mitochondria and the plasma membrane. This hypothesis is consistent with the fact that S1R is enriched in MCS between ER and mitochondria (Hayashi and Su, 2007; Zhemkov et al., 2021a), ER-PM junctions (Srivats et al., 2016; Zhemkov et al., 2021a) and ER-lipid droplets (Hayashi and Su, 2003). We further propose that the physical properties of these S1R domains, such as their high cholesterol content, higher rigidity and flat geometry can facilitate the initial formation of stable contacts between the ER membrane and membranes of other organelles. Indirect support to the hypothesis on microdomain-directed biogenesis of MCS comes from an observation of significant reduction in MAMs in S1R KO motor neurons (Watanabe et al., 2016). Direct support for this hypothesis will require time-resolved high-resolution imaging of ER movements as contact sites are formed and biochemical identification of MCS tethers that are enriched in S1R-formed ER microdomains. One potential implication of the proposed hypothesis is that it may help to explain why only a limited number of MCS are formed between ER and other organelles in cells. If formation of MCS require pre-existent cholesterol-rich ER microdomains, then the number of MCS in a given cell cannot exceed the total number of such microdomains in the ER.

Acknowledgments

We are thankful to Dr Meewhi Kim for useful discussions, to Dr Elena Vasileva for support and to Dr Mike Henne for comments on the manuscript. JL is a Sowell Family Scholar in Medial Research. IB holds the Carl J. and Hortense M. Thomsen Chair in Alzheimer's Disease Research.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Russian Science Foundation Grant 19-15-00184 (IB) and by the grants from the National Institutes of Health R01NS056224 (IB), R01AG055577 (IB) and R01GM113079 (JL).

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References

Albert S, Wietrzynski W, Lee CW, Schaffer M, Beck F, Schuller JM, Salome PA, Plitzko JM, Baumeister W, Engel BD (2020). Direct visualization of degradation microcompartments at the ER membrane. Proc Natl Acad Sci U S A *117*, 1069–1080.

Anastasia I, Ilacqua N, Raimondi A, Lemieux P, Ghandehari-Alavijeh R, Faure G, Mekhedov SL, Williams KJ, Caicci F, Valle G, et al. (2021). Mitochondria-rough-ER contacts in the liver regulate systemic lipid homeostasis. Cell Rep *34*, 108873.

Annunziata I, Sano R, d'Azzo A (2018). Mitochondria-associated ER membranes (MAMs) and lysosomal storage diseases. Cell Death Dis *9*, 328.

Area-Gomez E, Del Carmen Lara Castillo M, Tambini MD, Guardia-Laguarta C, de Groof AJ, Madra M, Ikenouchi J, Umeda M, Bird TD, Sturley SL, Schon EA (2012). Upregulated function of mitochondria-associated ER membranes in Alzheimer disease. EMBO J *31*, 4106–4123.

Bhattacharyya R, Barren C, Kovacs DM (2013). Palmitoylation of amyloid precursor protein regulates amyloidogenic processing in lipid rafts. J Neurosci *33*, 11169–11183.

Bhattacharyya R, Black SE, Lotlikar MS, Fenn RH, Jorfi M, Kovacs DM, Tanzi RE (2021). Axonal generation of amyloid-beta from palmitoylated APP in mitochondria-associated endoplasmic reticulum membranes. Cell Rep *35*, 109134.

Browman DT, Resek ME, Zajchowski LD, Robbins SM (2006). Erlin-1 and erlin-2 are novel members of the prohibitin family of proteins that define lipid-raft-like domains of the ER. J Cell Sci *119*, 3149–3160.

Carrasco S, Meyer T (2011). STIM proteins and the endoplasmic reticulum-plasma membrane junctions. Annu Rev Biochem *80*, 973–1000.

Chang CL, Chen YJ, Liou J (2017). ER-plasma membrane junctions: why and how do we study them? Biochim Biophys Acta Mol Cell Res *1864*, 1494–1506.

Cho KF, Branon TC, Rajeev S, Svinkina T, Udeshi ND, Thoudam T, Kwak C, Rhee HW, Lee IK, Carr SA, Ting AY (2020). Split-TurboID enables contact-dependent proximity labeling in cells. Proc Natl Acad Sci U S A *117*, 12143–12154.

Cohen S, Valm AM, Lippincott-Schwartz J (2018). Interacting organelles. Curr Opin Cell Biol *53*, 84–91.

Csordas G, Varnai P, Golenar T, Roy S, Purkins G, Schneider TG, Balla T, Hajnoczky G (2010). Imaging interorganelle contacts and local calcium dynamics at the ER-mitochondrial interface. Mol Cell *39*, 121–132.

Csordas G, Weaver D, Hajnoczky G (2018). Endoplasmic reticulum-mitochondrial contactology: structure and signaling functions. Trends Cell Biol *28*, 523–540.

Debattisti V, Gerencser AA, Saotome M, Das S, Hajnoczky G (2017). ROS control mitochondrial motility through p38 and the motor adaptor Miro/Trak. Cell Rep *21*, 1667–1680.

Friedman JR, Webster BM, Mastronarde DN, Verhey KJ, Voeltz GK (2010). ER sliding dynamics and ER-mitochondrial contacts occur on acetylated microtubules. J Cell Biol *190*, 363–375.

Garofalo T, Matarrese P, Manganelli V, Marconi M, Tinari A, Gambardella L, Faggioni A, Misasi R, Sorice M, Malorni W (2016). Evidence for the involvement of lipid rafts localized at the ER-mitochondria associated membranes in autophagosome formation. Autophagy *12*, 917–935.

Hajnoczky G, Csordas G, Yi M (2002). Old players in a new role: mitochondria-associated membranes, VDAC, and

ryanodine receptors as contributors to calcium signal propagation from endoplasmic reticulum to the mitochondria. Cell Calcium *32*, 363–377.

Hayashi T, Fujimoto M (2010). Detergent-resistant microdomains determine the localization of sigma-1 receptors to the endoplasmic reticulum-mitochondria junction. Mol Pharmacol *77*, 517–528.

Hayashi T, Su TP (2001). Regulating ankyrin dynamics: roles of sigma-1 receptors. Proc Natl Acad Sci U S A *98*, 491–496.

Hayashi T, Su TP (2003). Sigma-1 receptors (sigma(1) binding sites) form raft-like microdomains and target lipid droplets on the endoplasmic reticulum: roles in endoplasmic reticulum lipid compartmentalization and export. J Pharmacol Exp Ther *306*, 718–725.

Hayashi T, Su TP (2007). Sigma-1 receptor chaperones at the ER-mitochondrion interface regulate Ca(2+) signaling and cell survival. Cell *131*, 596–610.

Hayashi-Nishino M, Fujita N, Noda T, Yamaguchi A, Yoshimori T, Yamamoto A (2009). A subdomain of the endoplasmic reticulum forms a cradle for autophagosome formation. Nat Cell Biol *11*, 1433–1437.

Henne M (2019). And three's a party: lysosomes, lipid droplets, and the ER in lipid trafficking and cell homeostasis. Curr Opin Cell Biol *59*, 40–49.

Henne WM (2017). Discovery and roles of ER-endolysosomal contact sites in disease. Adv Exp Med Biol *997*, 135–147.

Hung V, Lam SS, Udeshi ND, Svinkina T, Guzman G, Mootha VK, Carr SA, Ting AY (2017). Proteomic mapping of cytosol-facing outer mitochondrial and ER membranes in living human cells by proximity biotinylation. Elife *6*, e24463.

Joshi AS, Zhang H, Prinz WA (2017). Organelle biogenesis in the endoplasmic reticulum. Nat Cell Biol *19*, 876–882.

King C, Sengupta P, Seo AY, Lippincott-Schwartz J (2020). ER membranes exhibit phase behavior at sites of organelle contact. Proc Natl Acad Sci U S A *117*, 7225–7235.

Kornmann B, Currie E, Collins SR, Schuldiner M, Nunnari J, Weissman JS, Walter P (2009). An ER-mitochondria tethering complex revealed by a synthetic biology screen. Science *325*, 477–481.

Kurokawa K, Nakano A (2019). The ER exit sites are specialized ER zones for the transport of cargo proteins from the ER to the Golgi apparatus. J Biochem *165*, 109–114.

Lee JE, Cathey PI, Wu H, Parker R, Voeltz GK (2020). Endoplasmic reticulum contact sites regulate the dynamics of membraneless organelles. Science *367*, 7108. doi: 10.1126/science.aay7108. PMID: 32001628.

Lorent JH, Diaz-Rohrer B, Lin X, Spring K, Gorfe AA, Levental KR, Levental I (2017). Structural determinants and functional consequences of protein affinity for membrane rafts. Nat Commun *8*, 1219.

Lynes EM, Bui M, Yap MC, Benson MD, Schneider B, Ellgaard L, Berthiaume LG, Simmen T (2012). Palmitoylated TMX and calnexin target to the mitochondria-associated membrane. EMBO J *31*, 457–470.

Mioka T, Guo T, Wang S, Tsuji T, Kishimoto T, Fujimoto T, Tanaka K (2022). Characterization of micron-scale protein-depleted plasma membrane domains in phosphatidylserine-deficient yeast cells. J Cell Sci *135*, jcs256529.

Mitra K, Ubarretxena-Belandia I, Taguchi T, Warren G, Engelman DM (2004). Modulation of the bilayer thickness of exocytic pathway membranes by membrane proteins rather than cholesterol. Proc Natl Acad Sci U S A *101*, 4083–4088.

Montesinos J, Pera M, Larrea D, Guardia-Laguarta C, Agrawal RR, Velasco KR, Yun TD, Stavrovskaya IG, Xu Y, Koo SY, Snead AM, Sproul AA, Area-Gomez E, The Alzheimer's disease-associated C99 fragment of APP regulates cellular cholesterol trafficking. EMBO J 39, e103791.

Morciano G, Marchi S, Morganti C, Sbano L, Bittremieux M, Kerkhofs M, Corricelli M, Danese A, Karkucinska-Wieckowska A, Wieckowski MR, et al. (2018). Role of mitochondria-associated ER membranes in calcium regulation in cancer-specific settings. Neoplasia *20*, 510–523.

Phillips MJ, Voeltz GK (2016). Structure and function of ER membrane contact sites with other organelles. Nat Rev Mol Cell Biol *17*, 69–82.

Poston CN, Krishnan SC, Bazemore-Walker CR (2013). In-depth proteomic analysis of mammalian mitochondria-associated membranes (MAM). J Proteomics *79*, 219–30.

Prinz WA, Toulmay A, Balla T (2020). The functional universe of membrane contact sites. Nat Rev Mol Cell Biol *21*, 7–24.

Quon E, Sere YY, Chauhan N, Johansen J, Sullivan DP, Dittman JS, Rice WJ, Chan RB, Di Paolo G, Beh CT, Menon AK (2018). Endoplasmic reticulum-plasma membrane contact sites integrate sterol and phospholipid regulation. PLoS Biol *16*, e2003864.

Raiborg C, Wenzel EM, Stenmark H (2015). ER-endosome contact sites: molecular compositions and functions. EMBO J *34*, 1848–1858.

Reane DV, Rizzuto R, Raffaello A (2020). The ER-mitochondria tether at the hub of Ca2+ signaling. Curr Opin Physiol *17*, 261–268.

Sano R, Annunziata I, Patterson A, Moshiach S, Gomero E, Opferman J, Forte M, d'Azzo A (2009). GM1-ganglioside accumulation at the mitochondria-associated ER membranes links ER stress to Ca(2+)-dependent mitochondrial apoptosis. Mol Cell *36*, 500–511.

Saotome M, Safiulina D, Szabadkai G, Das S, Fransson A, Aspenstrom P, Rizzuto R, Hajnoczky G (2008). Bidirectional Ca2+-dependent control of mitochondrial dynamics by the Miro GTPase. Proc Natl Acad Sci U S A *105*, 20728–20733.

Schon EA, Area-Gomez E (2013). Mitochondria-associated ER membranes in Alzheimer disease. Mol Cell Neurosci *55*, 26–36.

Scorrano L, De Matteis MA, Emr S, Giordano F, Hajnoczky G, Kornmann B, Lackner LL, Levine TP, Pellegrini L, Reinisch K, et al. (2019). Coming together to define membrane contact sites. Nat Commun *10*, 1287.

Shenkman M, Lederkremer GZ (2019). Compartmentalization and selective tagging for disposal of misfolded glycoproteins. Trends Biochem Sci *44*, 827–836.

Srivats S, Balasuriya D, Pasche M, Vistal G, Edwardson JM, Taylor CW, Murrell-Lagnado RD (2016). Sigma1 receptors inhibit store-operated Ca2+ entry by attenuating coupling of STIM1 to Orai1. J Cell Biol *213*, 65–79.

Szabadkai G, Bianchi K, Varnai P, De Stefani D, Wieckowski MR, Cavagna D, Nagy AI, Balla T, Rizzuto R (2006). Chaperone-mediated coupling of endoplasmic reticulum and mitochondrial Ca2+ channels. J Cell Biol *175*, 901–911.

van Vliet AR, Agostinis P (2018). Mitochondria-associated membranes and ER stress. Curr Top Microbiol Immunol *414*, 73–102.

Vance JE (2014). MAM (mitochondria-associated membranes) in mammalian cells: lipids and beyond. Biochim Biophys Acta *1841*, 595–609.

Vance JE (2020). Inter-organelle membrane contact sites: implications for lipid metabolism. Biol Direct *15*, 24.

Voeltz GK, Rolls MM, Rapoport TA (2002). Structural organization of the endoplasmic reticulum. EMBO Rep *3*, 944–50.

Wang X, Schwarz TL (2009). The mechanism of Ca2+ -dependent regulation of kinesin-mediated mitochondrial motility. Cell *136*, 163–74.

Wang X, Wen Y, Dong J, Cao C, Yuan S (2018). Systematic in-depth proteomic analysis of mitochondria-associated endoplasmic reticulum membranes in mouse and human testes. Proteomics *18*, e1700478.

Watanabe S, Ilieva H, Tamada H, Nomura H, Komine O, Endo F, Jin S, Mancias P, Kiyama H, Yamanaka K (2016). Mitochondria-associated membrane collapse is a common pathomechanism in SIGMAR1- and SOD1-linked ALS. EMBO Mol Med *8*, 1421–1437.

Yi M, Weaver D, Hajnoczky G (2004). Control of mitochondrial motility and distribution by the calcium signal: a homeostatic circuit. J Cell Biol *167*, 661–72.

Zhang H, Hu J (2016). Shaping the endoplasmic reticulum into a social network. Trends Cell Biol *26*, 934–943.

Zhemkov V, Ditlev JA, Lee WR, Wilson M, Liou J, Rosen MK, Bezprozvanny I (2021a). The role of sigma 1 receptor in organization of endoplasmic reticulum signaling microdomains. Elife *10*, e65192.

Zhemkov V, Geva M, Hayden M R., Bezprozvanny I (2021b). Sigma-1 receptor (S1R) interaction with cholesterol: mechanisms of s1r activation and its role in neurodegenerative diseases. Int J Mol Sci *22*, 4082.