Sigma 1 Receptor, Cholesterol and Endoplasmic Reticulum Contact Sites

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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 Ca²⁺ (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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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 (Hajnoczy et al., 2002; Csordas et al., 2018), ATP production (Hajnoczy 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 Arean-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 restricting 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\(_3\)R). It is known that InsP\(_3\)R 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\(_3\)Rs, specifically InsP\(_3\)R type 3, are also known to be enriched in MAM and colocalize with S1R (Hayashi and Su, 2007). S1R increases stability of the InsP\(_3\)R under resting conditions and activates InsP\(_3\)-induced Ca\(^{2+}\) 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 (Brownman 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
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). 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

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**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.
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.

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