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Remodeling of ER Membrane Contact Sites During Cell Division

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Abstract

Membrane contact sites (MCS) provide specialized conduits for inter-organelle communications to maintain cellular homeostasis. Most organelles are interconnected, which supports their coordination and function. M-phase (mitosis or meiosis) is associated with dramatic cellular remodeling to support cell division, including the equal distribution of organelles to the two daughter cells. However, the fate of MCS in M-phase is poorly understood. Here we review recent advances arguing for differential remodeling of endoplasmic reticulum (ER) MCS with the plasma membrane (PM, ERPMCS) and the mitochondria (MERCS) during cell division.

Keywords

membrane contact sites, MERCS, ERPMCS, mitosis, meiosis, cell division, endoplasmic reticulum, mitochondrion (mitochondria)

Introduction

Cellular homeostasis requires proper communication and coordination between different intracellular organelles. Organelles communicate by way of vesicular transport, diffusible intracellular messengers, and directly through physical association at Membrane Contact Sites (MCS). These three modalities operate on different time scales with the fastest being through MCS given their close physical association. MCS are close appositions between the membranes of different organelles (<30–50 nm apart) without fusion. They tend to be dynamic and are maintained by membrane tethers that link the two opposing membranes to stabilize MCS. MCS form signaling hubs that facilitate inter-organelle communications and have been best studied in the context of Ca^{2+} signaling and non-vesicular lipid transfer (Phillips and Voeltz, 2016; Prinz et al., 2019; Sassano et al., 2022; Scorrano et al., 2019; Voeltz et al., 2024). Recent evidence argues that MCS are disrupted in various diseases including neurodegeneration and cancer (Gil-Hernandez et al., 2020; Vrijsen et al., 2022), highlighting their importance in maintaining physiological homeostasis.

Although MCS occur between most organelles, the best understood are those involving the endoplasmic reticulum (ER), in particular with the plasma membrane (PM) and mitochondria. We refer to ER contact sites with the PM as ERPMCS and mitochondria to ER contact sites as MERCS. The ER forms an extensive, structurally diverse, and complex network of tubules and cisternae throughout the cell. Thus, it forms a natural hub for intracellular communication, including inter-organelle communication through MCS (Phillips and Voeltz, 2016), as it makes contacts with most other organelles including the mitochondria and PM (Wu et al., 2018).

Although it is clear by now that MCS are important signaling hubs, their fate during cell division is poorly understood. This is an important question to elucidate as organelles need to coordinate their remodeling during M-phase. Mitosis is the shortest phase of the cell cycle yet it is associated with the most dramatic structural alterations to produce two daughter cells that each needs to be viable independently. The sequential phases of the cell cycle are tightly governed by cyclin-dependent kinases (Cdks) in complex with cyclin proteins, with entry into mitosis driven by Cyclin B-Cdk1 (Nigg, 2001). The dynamic localization of additional kinases including Aurora A, Aurora B, and polo-like kinase 1 (PLK1) precisely regulate mitosis (Nigg, 2001). In addition, phosphatases, such as PP1 and PP2A as well as cell cycle-regulated ubiquitin ligases,

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particularly the anaphase-promoting complex/cyclosome (APC/C) contribute to the spatiotemporally control of organelle dynamics during cell division (Carlton et al., 2020). In addition, Ca^{2+} signals have been implicated in M-phase progression (Machaca, 2010; Nader et al., 2013; Nugues et al., 2022)

Organelles are inherited from the mother cell during cell division as they cannot be generated *de novo* in daughter cells. Hence, similar to the equal distribution of the genetic material during mitosis, organelles also need to distribute equally into the daughter cells. This is supported by pronounced remodeling of intracellular organelles, membranous compartments, and cytoskeletal elements during mitosis (Jongsma et al., 2015).

ER Remodeling in Mitosis

Organelle inheritance involves their remodeling, often fragmentation, to facilitate their equal distribution to daughter cells. The ER forms a network of interconnected sheets and tubules that spread across the entire cell (English and Voeltz, 2013; McCullough and Lucocq, 2005; Terasaki, 2000; Terasaki et al., 2001). During mitosis the ER distributes cortically in ring-like structures, as the center of cell is occupied by the spindle-chromosome apparatus. Furthermore, ER tubules, which typically localize to the cell periphery, restructure into cisternae or fenestrated sheets (Lu et al., 2009, 2011; Puhka et al., 2012; Puhka et al., 2007). The exact morphology of the ER in mitosis is debated in the literature, most likely due to differences among cell types and technical issues that could interfere with visualizing it (Lu et al., 2009, 2011; Puhka et al., 2012; Puhka et al., 2007).

One of the most dramatic alterations in ER structure during mitosis is the loss of the nuclear envelope (NE), which retracts into the ER due to the dissociation of nuclear lamins that support the NE during interphase (Schwarz and Blower, 2016). This allows for chromosome condensation, association with the spindle apparatus, and separation to the daughter cells during mitosis. Loss of the NE is associated with the redistribution of NE membrane proteins to the mitotic ER (Champion et al., 2017). As the mitotic ER separates into the daughter cells, its associated NE proteins allow for the reformation on the NE when the cells complete mitosis and enter interphase.

Further remodeling of the ER during mitosis is associated with regulation of its association with the microtubule (MT) network through CLIMP-63, a MT binding protein. Phosphorylation of CLIMP-63 in mitosis dissociates it from MT and leads to ER remodeling (Vedrenne et al., 2005). Consistently, in cycling *Xenopus* extracts the ER losses its association with the MT network in the mitotic phase (Wang et al., 2013). Association of the ER with the MT network during mitosis could be problematic as it would interfere with chromosome segregation. In addition to CLIMP-63, the ER membrane proteins REEP3 and REEP4 also modulate ER-microtubule interactions in mitosis. REEP4 was identified in an unbiased screen for membrane proteins that bind to microtubules. Knockdown of REEP3/4 leads to defective cell division that is associated with ER accumulation on the metaphase chromosomes (Schlaitz et al., 2013). These data show that the clearance of the ER from the metaphase spindle apparatus is important for proper mitosis progression and thus cell proliferation (Schlaitz et al., 2013). Furthermore, STIM1 phosphorylation has also been implicated in the association between the ER and MT network in mitosis, however these findings are somewhat controversial as discussed in details below.

Although the ER loses its association with the MT network in mitosis, it remains associated with the actin cytoskeleton (Moore et al., 2021). Disruption of actin cables in mitosis alters ER structure and its association with the mitochondrial network. This argues that the actin network maintains ER and mitochondria scaffolding in mitosis.

ERPMCS and Store-Operated Ca^{2+} Entry (SOCE)

ERPMCS are well-studied MCSs that have been shown to be particularly important for Ca^{2+} signaling and non-vesicular lipid transfer (Balla, 2018; Prinz et al., 2019; Saheki and De Camilli, 2017; Stefan, 2020; Wu et al., 2018). ERPMCS are stabilized by various proteins that localize to the junction and tether the two membranes in close proximity (10–25 nm) without fusion. These tethers include VAPs, E-Syt1/2/3, Junctophilin1/2/3/4, Nir2/3, ORP5/8, GRAMD1a/2a, STEP, TMEM24, Kv2.1, and STIM1. Given the dramatic remodeling of the ER in mitosis, one would expect alterations in ERPMCS. This is indeed the case as ERPMCS are significantly downregulated in mitosis with functional implications on Ca^{2+} signaling (Yu et al., 2019).

Store-operated Ca^{2+} entry (SOCE) is a primary Ca^{2+} influx pathway that is activated in response to ER Ca^{2+} store depletion following stimulation with agonists linked to phospholipase C (PLC). Agonists that target G-protein coupled receptors (GPCR) or tyrosine kinase receptors activate PLCs that hydrolyze PIP2 (Phosphatidylinositol 4,5-bisphosphate) at the PM producing diacylglycerol (DAG) and the diffusible second messenger IP_3 (inositol 1,4,5-trisphosphate). IP_3 binds to and gates IP_3 receptors at the ER membrane, which are Ca^{2+} release channels, resulting in Ca^{2+} depletion from the ER. This induces the clustering of the ER localized Ca^{2+} sensor STIM1 due to loss of Ca^{2+} bound to its luminal EF-hand (Luik et al., 2006; Prakriya and Lewis, 2015) (Figure 1). Clustered STIM1 translocates to preexisting ERPMCSs, where it is trapped through interactions between its terminal poly-Lys domain and PIP2 initially

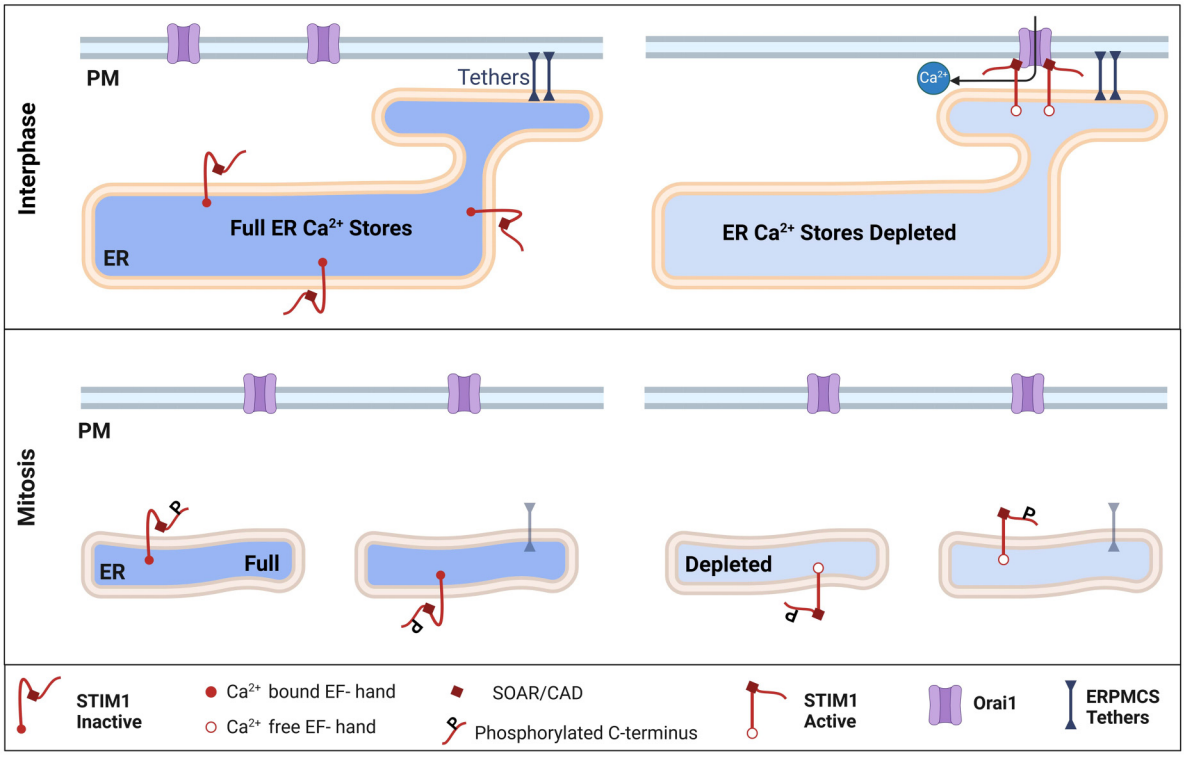

Figure 1. Store Operated Ca^{2+} Entry (SOCE) in Interphase and Mitosis. In interphase (Upper Panels) with full ER Ca^{2+} stores, STIM1 is diffuse throughout the ER in its inactive conformation. ERPMCS are stabilized by tethers that localize to the junctional interphase. Orai1 is diffuse at the PM. Ca^{2+} store depletion in response to agonist stimulation leads to a conformational change in STIM1 following loss of Ca^{2+} bound to its luminal EF-hand and exposure of the SOAR/CAD domain (red square) that interacts with and gates Orai1. Orai1 binding to STIM1 results in its trapping at ERPMCS. In mitosis (lower panels) the ER fragments and remodels resulting in the loss of ERPMCS and its positioning away from the PM. This physical separation prevents STIM1 from bridging the gap to the PM and interacting with Orai1. The C-terminal end of STIM1 is hyperphosphorylated in mitosis, however the functional correlates of this hyperphosphorylation remain unclear.

and then through binding to Orai1. STIM1 that is clustered at ERPMCS recruits Orai1, a PM localized Ca^{2+} channel, by diffusional trapping, resulting in Ca^{2+} influx into the SOCE microdomain delimited by the ER and PM bilayers at ERPMCS (Hodeify et al., 2015; Luik et al., 2006; Prakriya and Lewis, 2015) (Figure 1). Orai1 is highly Ca^{2+} selective and is gated by direct physical binding to STIM1 through its SOAR/CAD domain (Hogan, 2015; Lacruz and Feske, 2015; Prakriya and Lewis, 2015; Putney, 1986; Putney et al., 2017) (Figure 1). Multiple tools have been developed to image the distribution and dynamics of ERPMCS in the context of SOCE including fluorescently labelled ERPMCS tethers, tagged STIMs and Orais, as well as MAPPER (membrane-attached peripheral ER), which is an engineered construct that marks ERPMCS (Chang et al., 2013; Luik et al., 2006).

SOCE not only refills ER Ca^{2+} stores -thus preparing them for additional rounds of signaling- but also activates multiple downstream effectors (Prakriya and Lewis, 2015). Accordingly, SOCE mediates many physiological functions, including immune cell activation, muscle development, fluid secretion, and cell migration. This is somewhat surprising as ERPMCS are estimated to occupy only 1–4% of total PM area (Hogan, 2015), and the number of Orai1 channels that localize to the junctions following store depletion is small (estimated at 1–5 channels) (Hogan, 2015; Shen et al., 2021). Furthermore, Orai channels have a relatively small conductance and are inactivated by Ca^{2+}, thus limiting the amount of Ca^{2+} that enters the cell (Prakriya and Lewis, 2015). Ca^{2+} tunneling has been proposed as a mechanism to expand the spatial and temporal dimensions of the SOCE signaling microdomain. During tunneling, Ca^{2+} flowing through SOCE is directed to sites distal from the SOCE microdomain at ERPMCS allowing the activation of a larger number of distal effectors that do not localize to the limited SOCE microdomain at ERPMCS. Tunneling allows the uptake of Ca^{2+} flowing through SOCE by cortical SERCA pumps and its transport within the lumen of the ER to be released at distal sites through IP_3 receptors (Courjaret et al., 2018; Courjaret and Machaca, 2014, 2020; Petersen et al., 2017).

SOCE Inactivates in Mitosis

SOCE inactivates during M-phase in all cell types studied to date, including during mitosis of mammalian cells and meiosis of *Xenopus* and mouse oocytes (Lee et al., 2013;

Machaca and Haun, 2000, 2002; Preston et al., 1997; Preston et al., 1991; Smyth et al., 2012; Smyth et al., 2009; Tani et al., 2007; Volpi and Berlin, 1988; Yu et al., 2019; Yu et al., 2009). It has been proposed that SOCE inactivation during M-phase is important to prevent spurious Ca^{2+} signals that may derail its progression (Machaca, 2007; Nader et al., 2013). Maintaining functional SOCE during M-phase has not been easy to accomplish experimentally given the robust cellular machinery underlying its downregulation. However, existing evidence argues that a functional SOCE during cell division is deleterious. Overexpression of STIM1 and Orai1 in mouse oocytes is associated with increased Ca^{2+} influx during meiosis, which disturbs Ca^{2+} oscillations at egg activation and decreases the percent of zygotes that transition to the 2-cell stage with higher rates of fragmentation (Lee et al., 2013). Hence, artificially increasing SOCE disrupts the egg-to-embryo transition in mammals. This argues that SOCE inactivation during meiosis is important for meiosis completion in preparation for fertilization. Similarly, constitutive activation of SOCE during mitosis of mammalian cells leads to mitotic catastrophe and cell death (Yu et al., 2019). Interestingly, despite the requirement for Ca^{2+} influx to mediate proper egg activation at fertilization in mice (Miao et al., 2012), both STIM1 and STIM2 as well as Orai1 are not required. Mice with oocyte-specific conditional knockout (cKO) of STIM1, STIM2, or both, as well as Orai1-null mice are fertile with normal Ca^{2+} transients at fertilization (Bernhardt et al., 2017; Carvacho et al., 2018). This argues for other Ca^{2+} influx pathways in mammalian eggs to maintain Ca^{2+} oscillations.

In mitosis early studies showed inhibition of Ca^{2+} influx/SOCE (Preston et al., 1991; Tani et al., 2007; Volpi and Berlin, 1988). SOCE was also shown to completely inactivate during frog oocyte meiosis (Machaca and Haun, 2000, 2002). This SOCE inactivation was associated with hyperphosphorylation of STIM1 leading to its differential migration on SDS-PAGE in both mitosis and meiosis (Smyth et al., 2009; Smyth and Putney, 2012; Yu et al., 2009) (Figure 1). STIM1 contains 10 minimal Cdk-MAPK consensus sites (S/T-P), all located in the far C-terminal region. As Cdks/MAPKs are important for M-phase progression, this observation argued for an important role for STIM1 phosphorylation in SOCE inhibition during M-phase. However, in frog oocyte meiosis this was not the case, as the phosphorylation state of STIM1 at these residues did not affect SOCE (Yu and Machaca, 2022; Yu et al., 2009). Neither phosphomimetic nor Ala-substitution mutations at these residues affected SOCE inactivation during meiosis (Yu et al., 2009). In mitosis, overexpression studies of different STIM1 deletions and Ala-substitution mutants argued for a role for STIM1 phosphorylation in SOCE inactivation (Smyth et al., 2009). More recent evidence using endogenous STIM1 expression levels of a non-phosphorylatable STIM1 mutant among other approaches argues that STIM1 phosphorylation does not mediate SOCE inhibition in mitosis (Yu et al., 2019; Yu and Machaca, 2022), similar to what is observed in frog meiosis. These studies used a STIM1 knockin mouse line that replaced the endogenous wild-type STIM1 with STIM1 10A, a mutant with the 10 residues that match the Cdk1/MAPK minimal consensus in the C-terminal end of STIM1 mutated to Ala. So STIM1 10A cannot be phosphorylated on these residues (Hammad et al., 2021; Yu et al., 2019; Yu and Machaca, 2022). These mice develop normally with no apparent defects and primary cells under mitosis normally with the typical SOCE downregulation (Yu et al., 2019).

Remodeling of ERPMCS During Mitosis

Given the need for STIM1 and Orai1 to interact physically the close proximity of the ER and PM afforded by ERPMCS is critical for SOCE; and by extension for Ca^{2+} homeostasis and signaling (Balla, 2018; Prinz et al., 2019; Saheki and De Camilli, 2017; Stefan, 2020; Wu et al., 2018). This is similar to the requirement for close association of the sarcoplasmic reticulum and T-tubule membranes for excitation-contraction coupling in muscle cells (Franzini-Armstrong and Jorgensen, 1994; Porter and Palade, 1957).

Yue et al. showed, using MAPPER to label ERPMCS (Chang et al., 2013; Chen et al., 2019), that the density of ERPMCS decreases 16-fold in naturally occurring mitotic cells compare to cells in interphase (Yu et al., 2019). The expression of several ER-PM tethers (E-Syt1, ORP8 and Gramd2a) was unaltered in mitosis at the protein level. The downregulation of ERPMCS was confirmed at the ultrastructural level in Jurkat cells using electron microscopy (EM). For interphase cells, the PM and the closest ER tubule form contact sites, whereas in mitosis, the average distance between the PM and the closest ER is about 100 nm (Yu et al., 2019) thus preventing the formation of ERPMCS (Figure 1). This is consistent with a previous EM study on mitotic HeLa cells that showed peripheral ER being excluded from approaching the PM by cortical F-actin at a distance of 150–200 nm (McCullough and Lucocq, 2005). Most of the ER tubules in mitosis that are nearest to the PM run parallel to it with only a small portion forming ERPMCS (Yu et al., 2019). Therefore, most of the ER in mitotic cells is too far from the PM to allow for direct STIM1-Orai1 interactions (Figure 1). Given the physical separation between the ER and PM in mitosis STIM1 cannot interact with Orai1. This would explain the loss of SOCE observed in mitosis (Figure 1).

The ER network is organized into an interconnected complex of tubules and sheets that serves as a hub for intracellular communication. Mitotic entry is characterized by rapid cell rounding and cell type-dependent reorganization of the ER (Jongsma et al., 2015). It is thus important to understand how association between the ER and microtubules is regulated during mitosis. In addition to its role as an ER Ca^{2+} sensor, STIM1 binds microtubules through its cytoplasmic domain via a plus-end microtubule binding

protein, EB1 (Grigoriev et al., 2008). Smyth et al. proposed that STIM1 phosphorylation regulates ER exclusion from the mitotic spindle by modulating its microtubule binding based partly on overexpression of STIM1–10A, which leads to mis-localization of the ER to the spindle in mitosis (Smyth et al., 2012). Surprisingly though this was not associated with any mitotic defects or delays. In contrast, when the non-phosphorylatable STIM1–10A mutant is expressed at endogenous levels the ER partitions normally away from the spindle in mitosis (Hammad et al., 2021). In MEFs derived from the STIM1 10A mice that express only a non-phosphorylatable version of STIM1 at endogenous levels, there are no defects in ER partition or localization to the spindle (Hammad et al., 2021). Consistently, STIM1–10A knockin mice, grow and reproduce normally with no apparent defects (Yu et al., 2019). Together, these data argue that STIM1 phosphorylation does not play a role in modulating ER remodeling in mitosis. As mentioned above, other candidate linkers modulate ER-microtubule interactions in mitosis including CLIMP-63 and REEP3/4.

In addition to microtubules, the actin cytoskeleton is also likely to be involved in ERPMCS remodeling during mitosis. The PM is closely connected to the actin network, which undergoes dramatic reorganization in response to the rapid cell shape change during mitosis (Carlton et al., 2020). In fact, cortical actin has been implicated in maintaining the spatial distribution and stability of ERPMCS (Hsieh et al., 2017). During mitosis both hydrostatic pressure and surface tension increase dramatically (Chugh et al., 2017; Fischer-Friedrich et al., 2014; Stewart et al., 2011), to support cell rounding and division. Although the hydrostatic pressure increase is driven by osmotic pressure, the actomyosin cortex is required to support cell rounding against this pressure increase (Chugh et al., 2017; Stewart et al., 2011). The outward rounding force is maintained through metaphase by Cdk1-dependent mitotic phosphorylation of DIAPH1, which controls cortical actin polymerization (Nishimura et al., 2019). It is thus tempting to suggest that the thick cortical actin, that forms during mitosis to counter the internal hydrostatic pressure, could interfere with the maintenance of ERPMCS.

Mitochondria Remodeling in Mitosis

The mitochondria form a dynamic interconnected network that is balanced during interphase by fission and fusion events. Multiple remodeling events converge during mitosis to support mitochondrial inheritance to daughter cells, including their association with the cytoskeleton and their fragmentation. Mitochondrial fragmentation during mitosis depends on the activity of the dynamic-related GTPase Drp1, which localizes to the outer mitochondrial membrane during fission (Smirnova et al., 2001). Cdk1 phosphorylates Drp1 and this phosphorylation event is required to mediate mitochondrial fissions as expression of an non-phosphorylatable Drp1 mutant reduces mitochondrial fragmentation (Taguchi et al., 2007). In addition to Cdk1, another mitotic kinase, Aurora A, is also involved in mitochondrial fragmentation during mitosis. Aurora A phosphorylates the small Ras-like GTPase RALA leading to its colocalization with its effector RALBP1 and Drp1 to mitochondria, which facilitates Drp1 phosphorylation by Cdk1 and mitochondrial fission in mitosis (Kashatus et al., 2011).

Furthermore, the association of mitochondria with the cytoskeleton is altered during mitosis to facilitate their inheritance. In interphase mitochondria associate with the microtubule network through the action of the microtubule motors kinesin and dynein. This microtubule association is disrupted in mitosis in response to activation of the mitotic kinases Cdk1 and Aurora A leading to shedding of microtubule motors from mitochondria (Chung et al., 2016). Interestingly, fragmented mitochondria are pushed to the periphery of the dividing cell through their association with the growing tips of microtubules (Kanfer et al., 2015). This remodeling requires the mitochondrial protein Miro and the cytoskeleton-associated protein Cenp-F. In addition to microtubules, the actin-myosin network is also involved in mitochondrial partitioning during mitosis. Myo19, which is involved in mitochondrial movement in interphase, was also shown to be important for their proper partitioning in mitosis (Rohn et al., 2014). Furthermore, a dense mesh of actin cables assemble in the cortex of mitotic cells where they organize both the ER and mitochondria supporting their partitioning (Moore et al., 2021). Interestingly, actin filaments appear to assemble around mitochondria in mitosis forming comet-like structures that shuffle mitochondria across the cells presumably leading to their randomization and minimizing concentrated partitioning of potentially damaged mitochondria to one of the daughter cells (Moore et al., 2021).

Mitochondria ER Contact Sites (MERCS)

MERCS are membrane contacts between the mitochondria and smooth ER and represent one of the most abundant MCS given the relative sizes of the ER and mitochondrial networks. MERCS are involved in regulating various physiological and pathological functions, including Ca^{2+} signaling, energy homeostasis, redox biology, proteostasis, inflammation, and autophagy (Carreras-Sureda et al., 2022; Missiroli et al., 2018; Sassano et al., 2022; Yang et al., 2020). At MERCS the two membranes are usually 10–50 nm apart and are tethered by proteins that localize to the junction and stabilize it through protein-protein or protein lipid interactions (Rowland and Voeltz, 2012; Sassano et al., 2022). The tethers involved in MERCS include inositol 1,4,5-trisphosphate receptors, voltage-dependent anion channels (VDACs), the heat shock protein GRP75, mitofusin 2, VAPB, and PTPIP51 (Csordas et al., 2018; Sassano et al., 2022).

There is little known about the remodeling of MERCS in mitosis. As discussed above, the mitochondrial network

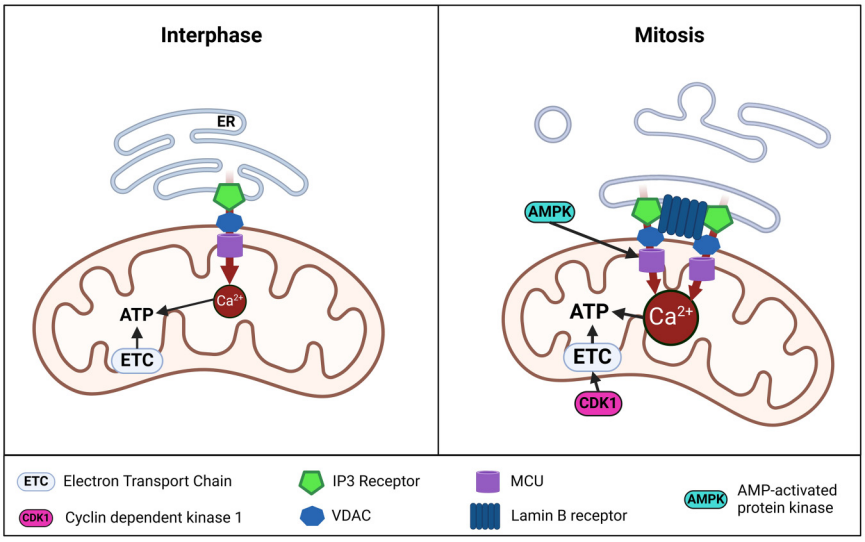

Figure 2. Remodeling of Mitochondria-ER Contact Sites (MERCS) in mitosis. In mitosis MERCS expand and their density increases due in part to the recruitment of the nuclear envelope protein Lamin B receptor (LBR). LBR interacts with the IP_3 Receptor on the ER membrane and VDAC on the outer mitochondrial membrane. MCU which is required for mitochondrial Ca^{2+} uptake on the inner mitochondrial membrane is phosphorylated in mitosis by the AMP-activated kinase (AMPK). The combination of increased MERCS and MCU phosphorylation increases mitochondrial Ca^{2+} transients in metaphase supporting increased ATP production to fuel mitosis progression. In addition, the primary kinase driving mitosis entry, cyclin-dependent kinase 1 (Cdk1) phosphorylates components of the electron-transport chain (ETC) in mitosis resulting in increased ATP production.

remodels during mitosis with the need to maintain mitochondrial functionality in terms of supporting the cell's energy demands, which are likely to be heightened during mitosis. As Ca^{2+} transfer at MERCS has been convincingly implicated in increasing mitochondrial respiration (Figure 2), the fate of MERCS in mitosis becomes of interest as it could affect mitochondrial respiration.

Yu et al. recently showed that MERCS expand during mitosis and that this expansion is functionally coupled to increased Ca^{2+} transfer into mitochondria in mitosis leading to enhanced mitochondrial dehydrogenase activity (Yu et al., 2024) (Figure 2). MERCS expansion was documented at the light microscopy level using MERCS markers; and at the ultrastructural levels using thin section EM, and serial EM coupled to 3D reconstruction. Functionally, Ca^{2+} imaging and NAD(P)H measurements supported increased Ca^{2+} transfer to mitochondria in mitosis to enhance dehydrogenase activity (Yu et al., 2024). These results argue that MERCS expand in mitosis to support the cell's energy needs in that phase of the cell cycle in a Ca^{2+}-dependent fashion (Figure 2).

The mitochondria also act as Ca^{2+} buffers as they modulate cellular Ca^{2+} transients, which have been associated with mitotic progression (Machaca, 2010; Nugues et al., 2022; Whitaker and Larman, 2001). Localized Ca^{2+} signals have been linked with mitosis, including Ca^{2+} transients during the metaphase to anaphase transition (Groigno and Whitaker, 1998; Poenie et al., 1986), and others at the centrosomes (Helassa et al., 2019). In contrast, entry into meiosis does not require a Ca^{2+} signal (Sun and Machaca, 2004; Tombes et al., 1992). Therefore, in addition to modulating the increased energy demands in mitosis, the enhanced ER-mitochondrial Ca^{2+} coupling could modulate the spatial and temporal properties of the Ca^{2+} dynamics to support proper progression of mitosis.

As mitochondria are the energy powerhouse of the cell they need to maintain their functionality during mitosis, in particular because the dramatic remodeling in mitosis likely presents elevated cellular energy needs (Salazar-Roa and Malumbres, 2017; Wang et al., 2014; Zhao et al., 2019). The mechanistic details of how cells regulate mitochondrial respiration in mitosis are beginning to emerge. Cdk1 activation in mitosis phosphorylates multiple subunits of complex I leading to increased mitochondrial respiration (Wang et al., 2014) (Figure 2). Cdk1 is essential for mitosis entry, and as such is ideally suited to coordinate oxidative phosphorylation with other aspects of mitotic progression. In metaphase, cells produce a rapid and dramatic mitochondrial Ca^{2+} transient that requires the mitochondrial Ca^{2+} uniporter (MCU) (Zhao et al., 2019) (Figure 2). MCU depletion eliminates this transient and causes mitotic delay. As cells enter mitosis, cellular ATP levels drop which activates the cellular energy sensor AMP-activated protein kinase (AMPK). AMPK translocates to the mitochondria and phosphorylates MCU in mitosis. MCU phosphorylation enhances mitochondrial Ca^{2+} uptake in metaphase resulting in increased ATP production to support mitosis progression (Zhao et al., 2019) (Figure 2).

More recently, the nuclear Lamin B receptor (LBR) has also been implicated in the metaphase specific mitochondrial

Ca^{2+} transient that regulates mitotic energetics (Zhao et al., 2024). Zhao et al. observed a similar metaphase-specific mitochondrial Ca^{2+} transient that depends on MCU (Zhao et al., 2019). Furthermore, Zhao et al. (2024) observed a similar increase in MERCS density and length in mitosis as previously reported (Yu et al., 2024). In search for mitosis specific MERCS tethers, they identified LBR as a nuclear envelope protein enriched in the mitotic ER and at MERCS (Figure 2). Immunoprecipitation of LBR pulls down both VDAC2 and the IP_3R. Finally deletion of LBR decreases MERCS and mitochondrial respiration, and prolongs the metaphase to anaphase transition (Zhao et al., 2024). These results supports a role for LBR in expanding MERCS in mitosis to increase mitochondrial respiration (Figure 2).

Conclusions

MCSs are remarkable microenvironments for inter-organelle communications supported by multiple families of tethers and the cellular cytoskeleton, and they play important roles in cellular signaling and homeostasis. The heterogeneous composition, spatial, and temporal dynamics of MCS in physiology and pathology have become one of the most exciting research areas in cell biology. Recent evidence discussed in this short review, argue that MCS are differentially regulated in mitosis to support the cellular signaling and energetic needs. Whereas ERPMCS are practically eliminated in mitosis, MERCS expand. This remodeling affects Ca^{2+} signaling in mitosis and cellular energetics with implications on mitotic progression.

Although these new exciting findings increase our understanding of the regulation of mitotic progression, they raise several questions in this budding field of research. What is the physiological significance of downregulating ERPMCS and expansion of MERCS for the fidelity of cell division? What are the molecular mechanisms involved in remodeling of MCS during mitosis? Are the signaling mechanisms aligned with the primary kinase/phosphatase cascades driving mitosis? Are MCS tether protein targeted? Is the cytoskeleton, particularly the actinomyosin network, involved? If yes how? Answers to these and other questions promise a better understanding of cell division and proliferation and is likely to further implicate MCS remodeling in these processes. This thus promises to be an exciting and promising area of future research.

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