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Phosphoinositide transport and metabolism at membrane contact sites

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Abstract

Phosphoinositides are a family of signaling lipids that play a profound role in regulating protein function at the membrane-cytosol interface of all cellular membranes. Underscoring their importance, mutations or alterations in phosphoinositide metabolizing enzymes lead to host of developmental, neurodegenerative, and metabolic disorders that are devastating for human health. In addition to lipid enzymes, phosphoinositide metabolism is regulated and controlled at membrane contact sites (MCS). Regions of close opposition typically between the ER and other cellular membranes, MCS are non-vesicular lipid transport portals that engage in extensive communication to influence organelle homeostasis. This review focuses on lipid transport, specifically phosphoinositide lipid transport and metabolism at MCS.

Keywords

Cholesterol; Extended-synaptotagmins; K_V2; Lipid transfer; Membrane contact sites; OSBP; Phosphoinositides; PI; PI(4)P; PI(4,5)P_2; TMEM24

1. Introduction

One of the defining features of eukaryotic cells is the presence of membrane-bound organelles that have been traditionally viewed as specialized platforms for the compartmentalization and regulation of defined subcellular tasks. However, it is now apparent that intracellular organelles do not work in isolation, but rather engage in extensive communication and signal exchange enabling the coordination of organelle responses to maintain cellular homeostasis. Two mechanisms that permit continuous organelle communication are through vesicular and non-vesicular trafficking [1–4]. The active process of vesicular trafficking interconnects most organelles and is mediated by a sequence of events involving the budding of the vesicles from a donor membrane, directed transport through the cytoplasm and their subsequent fusion with an acceptor membrane (Fig. 1A).

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Declaration of competing interest

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This continuous flow of membrane enables bulk transport of lipids and proteins through the cytoplasm from one organelle to another (Fig. 1B). A second form of communication is through non-vesicular transport of metabolites that occurs at regions of close apposition between two organelle membranes (Fig. 1C and D).

First identified in striated muscle cells as regions of close membrane juxtaposition between the plasmalemma and sarcoplasmic reticulum in the 1950's [5], interest in membrane contact sites (MCS) has increased dramatically in the past decade. Indeed, we now know that inter-organelle communication via MCS is extraordinarily extensive, with each organelle forming functional contacts between one or more neighboring organelles to tune many aspects of cellular physiology including lipid metabolism, membrane dynamics, cellular stress responses, autophagy, and organelle trafficking and biogenesis. Along with increased interest, the definition of a MCS has evolved from merely being regions where two organelles come into close apposition, to regions where two organelles physically interact, resulting in the transfer or transport of metabolites (typically lipids and Ca^{2+}) that alters the properties of each organelle [6–8].

The structural and functional importance of MCS for Ca^{2+} signaling was first detailed for excitation-contraction coupling at the dyads and triads of cardiac and skeletal myocytes. Here, L-type Ca^{2+} channels (Ca_V1) in the t-tubule invaginations of the sarcolemma are intimately positioned across from ryanodine receptors in the sarcoplasmic reticulum. For cardiac myocytes, action potential-stimulated openings of $Ca_V1.2$ channels allows Ca^{2+} to flow into the cytosol, down is concentration gradient, to initiate Ca^{2+}-induced Ca^{2+} release (CICR) from ryanodine receptors which ultimately leads to muscle contraction [9]. Unlike cardiac myocytes, excitation contraction coupling in skeletal muscle cells is dependent on the physical coupling between $Ca_V1.1$ channels and ryanodine receptors, which allosterically drives Ca^{2+} release from the sarcoplasmic reticulum following action potential-stimulated movement of the $Ca_V1.1$ voltage sensor [10–12]. These original characterizations provided the framework to understand and dissect Ca^{2+} signaling at other MCS. Indeed, our knowledge of the molecular details and functional importance of Ca^{2+} transfer at many other MCS has expanded significantly and includes store-operated Ca^{2+} entry at ER-PM MCS, IP_3R-VDAC at ER-mitochondria MCS and TRPML1 at ER-lysosome MCS [13–20].

In addition to Ca^{2+}, lipid transfer is a defining feature of MCS. Unlike proteins that contain specific motifs or chemical modifications that target and sort them to a defined location, lipids are not thought to intrinsically possess such localization signals. Therefore, it is perhaps surprising that organelle membranes have stereotyped lipid signatures. Such compartmentalization is generated and maintained through localization of metabolizing enzymes and inter-organelle lipid transport at MCS. First characterized in 1990 [21], lipid transport at MCS allows for local tuning of lipid composition in a more selective manner than vesicular trafficking. Although the presence of two closely apposed membranes may allow for the spontaneous transfer of some lipid species between membranes [22,23] (Fig. 1C), this process is energetically unfavorable and thus unlikely to make physiologically relevant contributions to lipid content [24]. Instead, most lipid exchange at MCS occurs through the combinatorial actions of lipid transport proteins (LTPs; Fig. 1D) that facilitate

the enrichment and/or depletion of specific membrane lipids. Moreover, it is becoming increasingly clear that MCS are not simply sites of lipid transport and exchange, but also sites of lipid metabolism that influence membrane identity and function to regulate various cellular processes.

We begin by discussing fundamental features/considerations of MCS before detailing the molecular identity of key proteins, their functional roles, and how they work collaboratively to shape phosphoinositide metabolism at organelle membranes.

2. General principles of lipid metabolism at MCS

Below some general principles of MCS are discussed. As our knowledge expands so does the complexity of each principle.

2.1. Endoplasmic reticulum – the intracellular conductor

As noted above, MCS allow metabolites, in the context of this review – lipids, to be efficiently transferred between cellular membranes. Central to this lipid transfer is the endoplasmic reticulum (ER), whose expansive membrane surface and key role in lipid metabolism perfectly position it to regulate the intracellular lipid landscape via MCS. The ER simultaneously forms MCS with many other organelle membranes, including the plasma membrane (PM), Golgi, mitochondria, lysosomes, endosomes, peroxisomes, and lipid droplets (LD) to influence organelle function [25,26]. As the central actor in this choreography, alterations in ER homeostasis directly influence the lipid content of many organelle membranes to tune membrane dynamics [27].

2.2. Basic architecture of MCSs

Lipid transport at MCS is mediated by LTPs which have multiple domains to simultaneously target and transport membrane lipids [1,28] (Fig. 1D). LTPs generally fall into one of two major categories, acting either as shuttles or tunnels/bridges to facilitate lipid movement through the cytosol between membranes. In both instances, LTPs have two localization signals to effectively target the protein to donor and acceptor membranes at specific MCSs and a hydrophobic cavity that shelters lipids as they journey through the cytoplasm. Targeting information is most often provided through the combinatory actions of (i) transmembrane domains or FFAT motifs (two Phe residues in an acidic tract), which interact with the ER membrane proteins VAMP-associated protein (VAP) family (VAPA and VAPB) [29–31], thereby mediating interaction with the ER membrane, and (2) lipid binding domains (such as PH or C2) which bind specific membrane lipids, typically negatively charged phosphoinositides, on non-ER membranes [32–35]. Thus, it is the code of membrane targeting (transmembrane domain, FFAT motif) and lipid signature (lipid binding domain) that recruits LTP to the correct MCS nanodomain (Fig. 1D). Once targeted to MCS, lipid transfer domains (examples include ORD, START, TULIP) can extract a lipid from membranes by holding the hydrophobic moiety of the lipid molecule in the interior of the domain and transferring or counter-transporting it between membranes to influence lipid environment [36]. In addition to these basic requirements, many LTPs can be allosterically regulated by phosphorylation, protein-protein interactions, or lipid

environment. An exhaustive description of all contact sites and the proteins that regulate them is well beyond the scope of this review, we refer the reader to the many excellent detailed reviews on this topic [6,37–41].

2.3. Rate of lipid transfer at MCSs

Information regarding intrinsic lipid transfer rates at MCSs has been difficult to extract as measurements are often indirect and represent a convolution of variables (e.g. lipid synthesis rate, transfer rate, metabolism rate). Given these difficulties, there aren't accepted kinetic rate constants for lipid transport in vivo. This said, there have been numerous calculations that estimate the rate and capacity of lipid transfer at MCS. Perhaps the best example comes from mitochondria which are disconnected from vesicular trafficking pathways and rely almost entirely on lipid transfer at MCS. Such bulk lipid transport at mitochondria has been estimated to transport ~20,000 phospholipids per second to support mitochondrial expansion [42]. Similar rates of lipid transfer have been reported during autophagosome maturation [43]. For LTPs involved in phosphoinositide metabolism such as OSBP [44], ORP5/8 [45], and TMEM24 [46] slower rates of lipid transfer have been reported perhaps reflecting more selective, rather than fast/bulk transport at MCS. Very likely, with technological developments, we may find that rates will be lipid- and membrane contact site-specific, and variable depending on metabolic demands of individual cells.

3. Intersection of phosphoinositide metabolism and lipid transport

We now focus our attentions on phosphoinositide metabolism at membrane contact sites. Phosphoinositides (PIs) are a family of negatively charged phospholipids that orchestrate and define organelle membrane identity. There are seven phosphoinositide species that are generated following phosphorylation of the parent phosphatidylinositol species at specific sites on its inositol ring to generate monophosphorylated PI(3)P, PI(4)P, and PI(5)P. Subsequently, these monophosphorylated lipids are substrates for specific lipid kinases to produce PI(4,5)P_2, PI(3,4)P_2, and PI(3,4)P_2, with PI(4,5)P_2 acting as the precursor for the sole triply phosphorylated PI(3,4,5)P_3 (Fig. 2A). It is the spatial and temporal actions of approximately 40 lipid kinases and phosphatases that facilitate the development of the phosphoinositide zip-code where each organelle membrane has a signature phosphoinositide species [47,48]. For example, the signature PI at the PM is PI(4,5) P_2 where its negatively charged headgroup electrostatically recruits cytosolic proteins to the PM (such as adapter proteins to orchestrate membrane fusion events [49]) or binds to membrane proteins (such as ion channels [50–52]) to alter their function. Underlying the importance of regulated phosphoinositide metabolism, mutations in lipid kinases or phosphatases lead to a host of devastating disorders including Parkinson's disease, Lowe syndrome, Dent disease, Charcot-Marie-Tooth Disease and Amyotrophic Lateral Sclerosis (for review see [47,53–56]). In addition to lipid metabolizing enzymes, it is now clear that membrane contact sites represent portals that influence and define phosphoinositide species at organelle membranes. Best studied for ER-PM [35,45,46,57–62], ER-Golgi MCS [32,44,63], and ER-endo/lysosome MCS [64–67](Fig. 2B–E), it is likely that all MCS are hubs for phosphoinositide metabolism. We now discuss each of these MCS and the role they play in shaping phosphoinositides at organelle membranes.

4. Phosphoinositide metabolism at ER-PM: maintenance of plasma membrane PI(4,5)P_2

ER-PM junctions have been the most extensively studied MCS. In terms of lipid transport, the overarching role of ER-PM MCS is to maintain the plasma membrane PI(4,5)P_2 necessary for ion channel function, endocytosis, actin cytoskeleton organization, and other PI(4,5) P_2-dependent signaling reactions. To do so, two phosphoinositide species, PI and PI(4)P, are transferred or countertransported at ER-PM MCS [45,46,61] (Fig. 2C). We begin by detailing the molecular identities of proteins involved in PI transport at ER-PM MCS, before moving to PI(4) P, the precursor of PM PI(4,5)P_2.

4.1. TMEM24

Anchored at the ER membrane through its transmembrane domain, TMEM24 (also known as C2CD2L) interacts with the PM through electrostatic interactions of its C2 domain with negative charged PM phospholipids [46,68](Fig. 2C). In addition to these two localization signatures, TMEM24 also has a lipid transport module called a SMP (synaptotagmin-like, mitochondrial and lipid-binding protein) domain which is a lipid-binding module of the tubular lipid-binding (TULIP) superfamily [46]. This lipid binding module harbors glycerolipids, with a bias toward inositol phospholipids, especially PI. At ER-PM MCS, the SMP domain of TMEM24 facilitates the transport of PI from its major site of synthesis, the ER, to the PM where it participates in replenishment of PM PI(4,5)P_2 [46,68]. Studies from pancreatic β-cells and neurons reveal that TMEM24 is predominantly bound to the PM at rest but un-couples following Ca^{2+}-dependent phosphorylation [69,70]. Such dynamic localization at ER-PM MCS presents a model wherein TMEM24 is engaged with the PM at rest to transfer PI from the ER to the PM, maintaining the pool of PM phosphoinositides, including PI(4)P and PI (4,5)P_2. Opening of voltage-dependent Ca^{2+} channels would then facilitate phosphorylation of the C-terminal region of TMEM24 (potentially via PKC) to disengage it from the PM to transiently abolish PI transfer [46]. Dephosphorylation of TMEM24 C-terminal by the S/T-phosphatase calcineurin/PP2B has been proposed to allow its reassociation to the PM [46]. Thus, the dynamic interplay between voltage-gated Ca^{2+} entry and protein kinases and phosphatases appear to tune PI transfer at ER-PM MCS of excitable cells.

4.2. NIR2/3

Membrane-associated phosphatidylinositol transfer protein 1 and 2 (NIR2/3) are cytosolic proteins that mostly localize to the cytoplasm and Golgi under resting conditions. Following G_q protein-coupled receptor (G_qPCR) activation to deplete PM PI(4,5)P_2, Nir2 and Nir3 are dynamically recruited to ER-PM MCS through FFAT-dependent interactions with the ER resident protein VAPA/B and binding of their C-terminal LNS2 domains to PM phosphatidic acid (PA; Fig. 2C) [71–73]. At ER-PM MCS Nir2 and Nir3 serve as important components of the phosphoinositide cycle by delivering PI from the ER to the PM to support the replenishment of PM PI(4,5)P_2 while simultaneously transporting PA in the opposite direction (Fig. 2C).

4.3. K_V2 channels

Voltage-dependent potassium channels of the K_V2 family, $K_V2.1$ and $K_V2.2$, are broadly expressed in excitable cells like neurons and smooth muscle cells, and play a fundamental role in regulating intrinsic electrical excitability [74]. In addition to regulating the electrical properties of cellular membranes, K_V2 channels have a propensity to accumulate in non-conducting clusters that form ER-PM MCS [75–79]. Through interactions with ER resident proteins VAPs [80,81], PM K_V2 channels generate ER-PM MCS that recruit the lipid transfer protein Nir2 to transport the PI to the PM that is required to sustain PM $PI(4,5)P_2$ levels (Fig. 2C) [82]. The regulation of K_V2 clusters is extremely dynamic and governed by the phosphorylation status of the channel, with cyclin-dependent kinase 5 (CDK-5) phosphorylating specific serine residues to induce ER-PM MCS formation, while calcineurin-dependent dephosphorylation disperses clusters [83,84]. Thus, the phosphorylation status of K_V2 channels allows it to be a bidirectional rheostat for both excitability and lipid metabolism. The importance of K_V2 channels in the physiological control of excitability and phosphoinositide metabolism is perhaps best described in the context of G_qPCR activation. Following neurotransmitter or hormone binding to G_q-coupled receptors, phospholipase C activation may lead to net depletion of PM $PI(4,5)P_2$ and depression of $PI(4,5)P_2$-dependent ion channels (e.g. $K_V7.2/7.3$ [85,86]). Decrease in $K_V7.2/3$ channel currents, which are crucial in setting the resting membrane potential of many neurons, would result in membrane depolarization [87–89]. If the resulting depolarization reaches threshold, action potential firing will trigger opening of voltage-gated Ca^{2+} channels (Ca_V) to increase intracellular Ca^{2+} levels. Elevations in cytoplasmic Ca^{2+} will activate calcineurin and trigger dispersal of K_V2 channels to increase the fractional proportion of conducting K_V2 channels available to dampen excitability. As action potential firing is depressed, CDK-5 phosphorylation would cluster K_V2 channels and recruit Nir2/3 to transfer PI to the PM to resynthesize PM $PI(4,5)P_2$ and once more activate $PI(4,5)P_2$-dependent ion channels. In addition to Nir2, K_V2 channels also interact with numerous other proteins, including Ca_V1 channels and ryanodine receptors (RyR) at somatic ER-PM MCS [77], therefore in addition to the electrical and lipid properties of cellular membranes, K_V2 channels are also key regulators of Ca^{2+} signaling nanodomains.

4.4. ORP5/8

Oxysterol-binding protein-related protein 5 and 8 (ORP5, ORP8) are lipid transport proteins found at multiple MCS, including ER-PM, ER-mito, ER-lysosome, and ER-lipid droplets [90–93]. ORP5 and 8 are localized at ER-PM MCS through C-terminal ER transmembrane domains and N-terminal PH domains that recognize and interact with negatively charged PM phosphoinositide lipids [45] (Fig. 2C). At ER-PM MCS the ORD (OSBP-related) domain of ORP5/8, with its typical hydrophobic pocket and lid structure [61], extracts and transports PM PI(4)P and ER PS through a counter-flow exchange mechanism [45]. Specifically, the counter transport cycle relies on a steep PI(4)P gradient between the PM (high PI(4)P levels) and ER (low PI(4)P levels) to transport PI(4)P from the ER to PM in exchange for phosphatidylserine (PS) moving in the opposite direction (Fig. 2C). The steep PI(4)P gradient that provides the energy for this counter exchange is maintained by the ER lipid phosphatase, SAC1, that dephosphorylates PI(4)P to PI on ER membranes (Fig. 2C). At rest ORP5/8 is localized to ER-PM MCS where they negatively regulate PM PI(4)P and

$PI(4,5)P_2$ levels. Under conditions of reduced PM PI(4)P or $PI(4,5)P_2$, ORP5/8 disengages from the PM to allow replenishment of phosphoinositide levels. Once PM phosphoinositide levels are restored, ORP5/8 reengage to provide an inhibitory brake against $PI(4)P/PI(4,5)P_2$ accumulation. There is also evidence that ORP8 can directly transport $PI(4,5)P_2$ from the PM to ER [61], once more providing a mechanism to negatively regulate phosphoinositide levels.

4.5. Extended synaptotagmins

There are 3 extended synaptotagmin isoforms in mammalian cells (E-Syt1, 2, 3) that act as ER-PM tethers and lipid transfer proteins [35]. Structurally, extended synaptotagmins are characterized by an N-terminal hydrophobic hairpin anchor that localizes it to ER membranes, a lipid harboring SMP domain, and multiple C2 domains that mediate electrostatic interactions with PM $PI(4,5)P_2$ (Fig. 2C) [57]. E-Syt2 and E-Syt3 are localized to the PM at steady-state, whereas E-Syt1 interacts with the PM under conditions of elevated intracellular Ca^{2+} [35,58]. E-Syts form homo and heterodimers through dimerization of their SMP domains to form an ~10 nm long hydrophobic groove that harbors glycerolipids, including DAG [60]. Heterodimerization of E-Syt1 to either of the other two isoforms may be expected to confer some Ca^{2+} sensitivity. Such Ca^{2+} sensitivity would provide a further layer of control to E-Syt localization. Functionally, cells lacking all three isoforms have excess DAG at the PM, therefore it seems that E-Syts are not only ER-PM membrane tethering proteins, but also part of a homeostatic control mechanism that transfers excess DAG from the PM to the ER to (i) limit PM phosphatidic acid generation, and (ii) allow for recycling of DAG back to the ER where it could potentially be metabolized into PI to perpetuate the phosphoinositide cycle [35,57,58,94,95] (Fig. 2C).

5. Phosphoinositide metabolism at ER-Golgi MCS

The signature phosphoinositide at the Golgi is PI(4)P. Generated through the actions of PI4KIIα [65,96] and PI4KIIIβ [65,97] on Golgi-localized PI [98], Golgi PI(4)P levels are important for orchestrating vesicular trafficking, membrane budding and fusion events, as well as maintaining PM $PI(4,5)P_2$ [99,100]. In addition to PI4Ks, Golgi PI(4)P is also regulated by Oxysterol-binding protein 1-dependent (OSBP) lipid transfer at ER-Golgi MCS. Structurally, OSBP has a N-terminal PH domain that binds Golgi PI(4)P in an ARF1-dependnet manner, and a C-terminal FFAT motif that binds VAP on ER membranes [32]. Once localized to ER-Golgi MCS, the ORD domain of OSBP is positioned to transfer PI(4)P to ER membranes in exchange for sterol moving to Golgi membranes (Fig. 2D) [44,101]. This counter transport cycle proceeds due to ORD having a higher affinity for PI(4)P than sterol. When at the Golgi, ORD can extract PI(4)P and transport it to the ER, where it is subsequently dephosphorylated by the PI(4)P 4-phosphatase SAC1. This dephosphorylation step is crucial, as it decreases ER PI(4)P and increases the affinity of ORD for ER sterol enabling it to now extract and harbor a sterol molecule for transport to the Golgi. Thus, it is the steep PI(4)P gradient (high in Golgi membranes, low in ER) that fuels the counter transfer of sterol against its concentration gradient (low in ER membranes) [32,44,102,103]. The model detailed above positions SAC1 acting in *cis* as a key regulator of this PI(4)P/sterol counter transport cycle. Recent work has provided evidence that the PI(4)P adaptor

protein (FAPP1), which interacts with VAPs and SAC1 at ER-TGN MCSs, can act as a sensor of TGN PI(4)P and promote *trans* activity of SAC1 across the ER-TGN contact sites to consume PI(4)P at the TGN [63]. Another key regulator of SAC1 at ER-TGN MCS is the carnitine palmitoyl-transferase 1C (CPT1C) [104]. Localized to the ER of neurons, CPT1C is a sensor of malonyl-CoA, an intermediate in the de novo synthesis of long-chain fatty acids whose levels fluctuate depending on the energy status of cells. Under steady-state conditions, CPT1C negatively regulates SAC1 activity to maintain 'normal' Golgi PI(4)P levels. However, under low malonyl-CoA levels, such as during glucose depletion, CPT1C-dependent inhibition of SAC1 is released, facilitating SAC1's trans-location to ER-TGN contact sites to decrease TGN PI(4)P [104].

In addition to mechanisms that influence SAC1 activity over physiological ranges, OSBP countercycle and Sac1 localization can be altered in disease. An example of altered lipid transfer at ER-Golgi MCS has recently been reported for neurodegenerative Niemann Pick C1 disease (NPC) [65]. In NPC, mutations in the lysosomal NPC1 cholesterol transporter reduce cholesterol egress from lysosomal membranes initiating a signaling cascade that recruits PI4KIIα and PI4KIIIβ to TGN membranes. Increases in TGN PI4K localization produces excess PI(4)P which recruits additional OSBP to enhance PI(4)P transport at ER-Golgi MCS [65]. Therefore the OSBP PI(4)P/sterol countertransport cycle can be tuned to control Golgi PI(4)P depending on protein expression, energy status of cells, or health of cells.

Finally, highlighting the complex regulation of OSBP at ER-Golgi MCS, it has recently been demonstrated that the IP_3 5-phosphatase, INPP5A, plays a critical role in controlling the localization of OSBP at ER-Golgi MCS through Ca^{2+}-induced dissociation of OSBP from the Golgi complex [105]. Given the intimate link between lipid transport and Ca^{2+} signaling at MCS perhaps all LTPs can be regulated by alterations in local Ca^{2+} concentrations either directly or indirectly through Ca^{2+}-dependent phosphorylation.

6. Phosphoinositide metabolism at ER-lysosomes/endosomes MCS

Endosomes and lysosomes contain a diverse complement of phosphoinositide's in their membranes including PI(4)P, PI(3,4)P_2, PI(4,5)P_2, as well as the signature isoforms, PI(3)P and PI(3,5)P_2. At endolysosomal membranes phosphoinositides serve a variety of functions including organelle transport, fission and fusion events, cholesterol transport, and control of Ca^{2+} signals (for review see [106–109]). The best characterized proteins that influence phosphoinositide levels at ER-endo-lysosome MCS are OSBP and ORP1L. Similar to what is described above at ER-Golgi MCS, OSBP appears to play an essential role in transferring cholesterol from the ER to the cytosolic leaflet of the lysosome membrane [64]. The mechanism through which it transports cholesterol also appears to be conserved between MCS, with VAP-FFAT interactions localizing OSBP to ER membranes and PI(4)P on lysosomes engaging the PH domain of OSBP to position the ORD domain at MCS for lipid transport (Fig. 2E) [65]. Under resting conditions OSBP seems to transport cholesterol from the ER to the lysosome as its inhibition abrogates the accumulation of cholesterol on lysosomal membranes [64]. OSBP-mediated cholesterol transfer at ER-lysosome MCS appears crucial for triggering aberrant mTORC1 signaling in NPC disease,

a condition were excess cholesterol in the cytoplasmic leaflet of lysosome membranes drives constitutively active mTORC1 activity [110], as OSBP inhibition abolishes deviant mTORC1 signaling and restores autophagic function [64]. Supporting the concept that PI(4)P is the phosphoinositide species that anchors OSBP at lysosomal membranes to participate in this countertransport cycle, PI(4)P, OSBP, VAPA, and SAC1 all increase at lysosomal membranes in NPC1 loss of function cells [65]. Collectively, these data provide new insight into the trafficking/transport routes of LDL-derived cholesterol and inform the following model: (i) LDL-derived cholesterol is transported out of the lysosome lumen through interactions between NPC1-NPC2; (ii) cholesterol transported across the lysosome membrane by NPC1 does not accumulate on lysosomal membranes but rather is rapidly picked-up and transported out of the lysosome (perhaps via ORP5, STARD3, or ORP1L) to the PM [111]; (iii) once PM cholesterol needs have been met, cholesterol is then redistributed to other organelles, including the ER; (iv) VAP–OSBP–PI (4)P return cholesterol to the lysosomal surface, across ER–lysosome MCS, to influence mTOR signaling, autophagy, and lysosomal positioning.

In addition to OSBP, ORP1L has been extensively studied at ER-endo/lysosome MCS and while the importance of this protein for regulating organelle positioning and function is clear [66,112–116], the precise molecular mechanism through which it operates to act as a cholesterol sensor/transporter and/or influence phosphoinositide metabolism is controversial and remains to be confirmed. ORP1L contains a PH domain and an oxysterol-binding-related domain (ORD) that is capable of binding sterols in vitro [117]. Under conditions of replete endosomal cholesterol ORP1L interacts with a complex that includes RAB7 GTPase, RILP (RAB-interacting lysosomal protein), the HOPS tethering complex (homotypic fusion and vacuole protein sorting), and the dynactin–dynein motor complex, resulting in minus-end-directed late endosome trafficking [113,114]. Conversely, under conditions of low endosomal cholesterol, the FFAT domain of ORP1L is released and free to bind VAP. This cholesterol-dependent conformational change in the local ORP1L interactome seems to serve two major purposes; (i) it reduces dynein-facilitated minus-end trafficking, and (ii) alters the transport ability/direction/rate of ORP1L. The later proposition remains to be explicitly tested as the precise molecular mechanisms of how ORP1L influences cholesterol transfer are still being unraveled. This is in part due to the ORD domain of ORP1L being able to harbor a variety of lipids including cholesterol, oxysterols, and phosphoinositides [117,118]. In vitro, the ORD domain of ORP1L transports cholesterol between liposomes [118,119], however it remains to be confirmed if this transport requires a phosphoinositide countertransport gradient in vivo (Fig. 2E), with some groups detailing ORP1L can bind and extract PI (4)P [118], while others suggest endo/lysosomal phosphoinositides, PI (3,4)P_2 and PI(4,5)P_2, act allosterically to regulate the targeting and cholesterol extraction ability of the ORD domain to enhance cholesterol transport [119]. Thus, ORP1L can facilitate transfer of cholesterol and potentially phosphoinositides at the LEL-ER interface. The involvement of phosphoinositide transfer remains to be confirmed and may well depend on the nutritional state and/or growth stages of the cell.

7. Phosphoinositide transport at other ER-organelle MCS

In addition to the best characterized MCS noted above, it seems that every organelle is likely to form MCS with at least one other neighboring membrane. As our knowledge of new MCS and the molecular elements that choreograph their function expand, a putative role for phosphoinositide species as central players in MCS protein engagement and regulation of key metabolite transport may emerge. For example, recent evidence demonstrates that ORP5-mediated PS/PI(4)P countertransport at ER-lipid droplet MCS is important for controlling lipid droplet size [93]. Additionally, ORP5/8 has been noted to localize to ER-mitochondria through interactions with the mitochondrial protein PTPIP51 to control mitochondrial morphology and function. Likely, PS is transferred from the ER to mitochondria by ORP5/8 therefore it seems possible that a phosphoinositide species may be transported in the opposite direction like what occurs at ER-PM and ER-LD MCS. This idea is further supported by the presence of PI on mitochondrial membranes [98].

8. Future questions/directions

Our knowledge of MCS has exploded over the last ten years and shows no signs of abating. With development of new techniques to visualize, characterize and interrogate structure/function relationships it seems inevitable our view of MCS physiology will become increasingly complex and crucial for understanding how cellular metabolism is regulated. Some of the overarching thoughts that may expand our view of phosphoinositide metabolism at MCS include, (i) how promiscuous are lipid transporting proteins between MCS? For example, ORP5/8 has been reported to play an important role at ER-PM, ER-lysosome, ER-mitochondria, and ER-LD, does each MCS have its own private, constant pool of ORP5/8 or does the fractional amount at each MCS change depending on cellular demand? (ii) How do transporters within the same MCS coordinate/integrate signals? Are there cooperative, allosteric interactions between transporters? (iii) More experiments need to be performed in primary cells to determine the cellular heterogeneity of MCS. Currently, most experiments are conducted in yeast or mammalian expression system cells, yielding invaluable and fundamentally important information. However, it seems likely that not all cells possess the full complement of MCS proteins, therefore expanding our knowledge into primary cells is crucial. (iv) How do MCS integrate information to choreograph inter-organelle responses. For example, how does NPC1-mediated cholesterol transport at ER-lysosome MCS influence cholesterol/phosphoinositide transport at ER-Golgi, ER-LD, ER-PM MCS. (v) How are MCS proteins altered in, and potentially contributing to, human disease? (vi) Can we leverage our knowledge of MCS to create better pharmacological agents to target specific MCS proteins, such as been already detailed for the antiproliferative ORPphilin which target OSBP [120].

9. Conclusions

As the study of MCSs continues to mature, our focus will undoubtedly shift from characterizing MCSs and tethers to understanding how their functions shape inter-organelle communication under different cellular conditions, including disease. For cellular metabolism, it is essential that we understand how stimuli, such as receptor activation, stress,

eating, or exercise influence MCS function at the cellular level and how these signals might integrate broader signaling and transcriptional programs to alter cellular, tissue, and systems homeostasis. Information gleaned from mutations of MCS components or phosphoinositide metabolizing enzymes [121–123], that cause Mendelian genetic disorders suggests they may play important roles in the development/progression of a broad range of pathophysiological conditions, including metabolic disorders, neurodegeneration, and aging. The last decade has established a strong framework to begin studying MCS composition and function in the context of health and disease.

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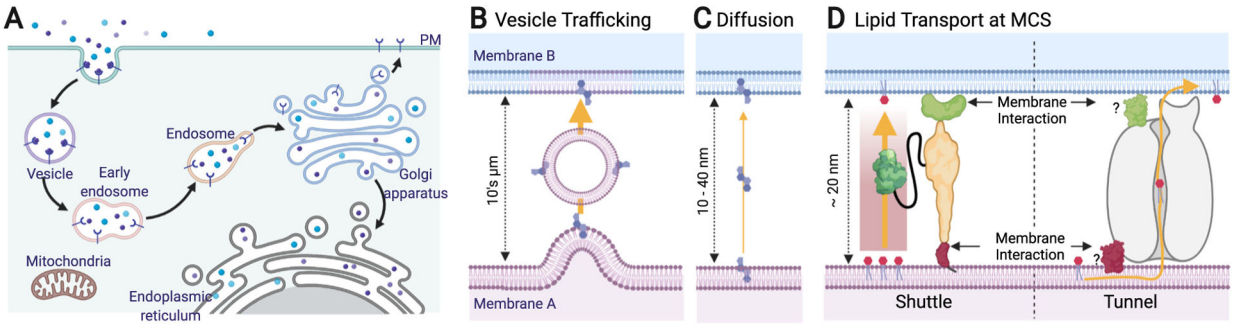

Fig. 1.

Mechanisms of intracellular lipid exchange. A. Vesicular transport (black arrows) facilitates communication, as well as protein and lipid exchange between organelles. B. Lipid transport by vesicular trafficking. C. Energetically unfavorable lipid diffusion at MCS. D. Two mechanisms of lipid transport at MCS. Left: Shuttling, lipid transport by a lipid transport protein (LTP) that shuttles a lipid from membrane A to membrane B down it's concentration gradient. Note the LTP is localized to the MCS through specific interactions at each membrane. B. Right: lipid transport via bridging or tunneling at MCS.

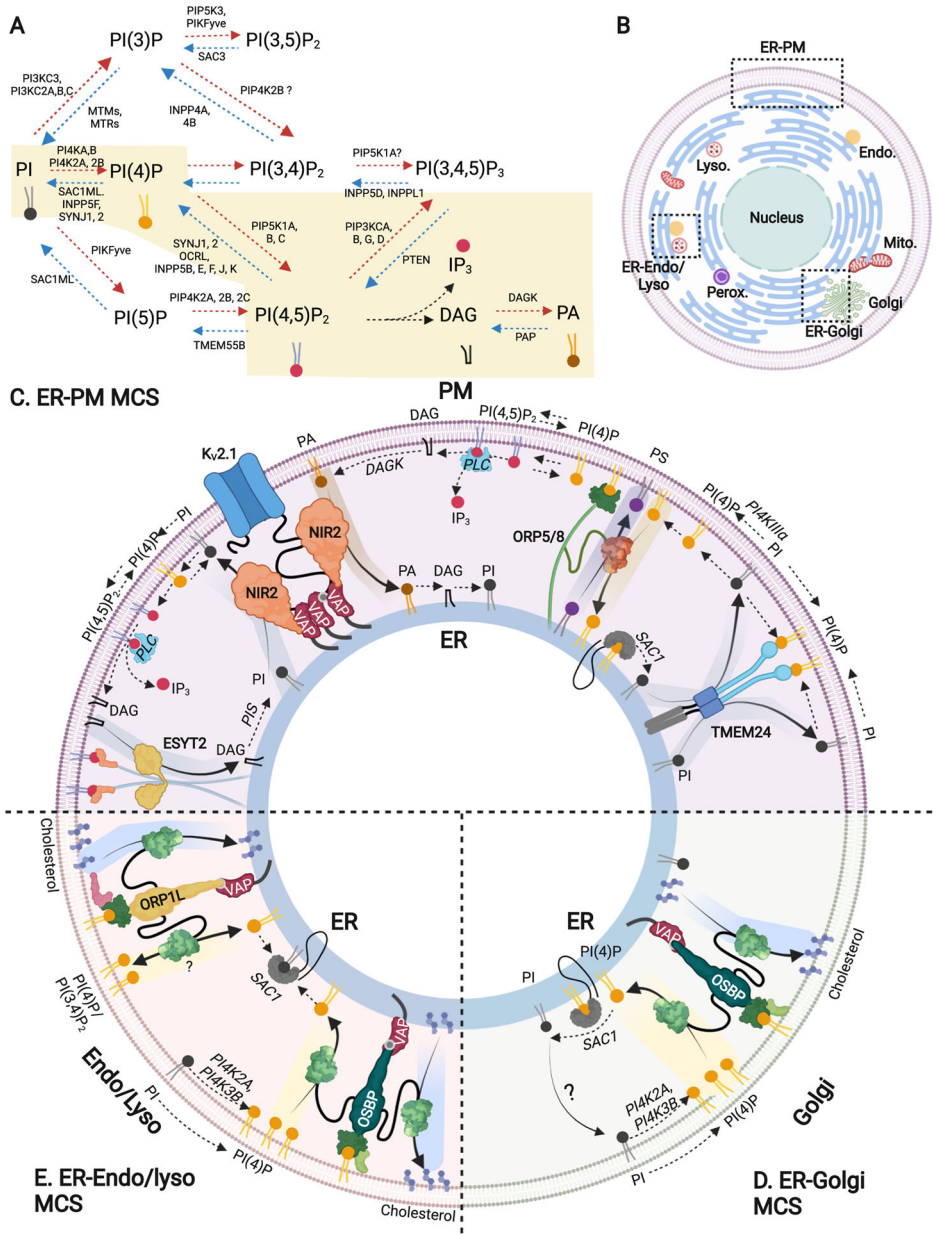

Fig. 2.

Phosphoinositide metabolism at membrane contact sites. A. Reaction scheme of phosphoinositide biogenesis. Red arrows present phosphoinositide lipid kinase reactions and blue arrows are phosphoinositide lipid phosphatases. Adjacent to each arrow are the gene names of each enzyme capable of catalyzing each reaction. Genes marked with ? represent enzymes with ambiguity surrounding their ability to catalyze those specific reactions. Yellow area is those phosphoinositide species discuss in this review. B. Schematic diagram of a mammalian cell depicting several organelles in proximity with the endoplasmic reticulum. Dashed rectangles represent those MCS discussed in this review. C–E. Molecular identity of the proteins involved in phosphoinositide metabolism at ER-PM (C), ER-Golgi

(D), and ER-endo-lysosome (E). MCS correspond to the dashed rectangles in B. Solid arrows represent lipid transfer, dashed arrows represent enzymatic reactions.