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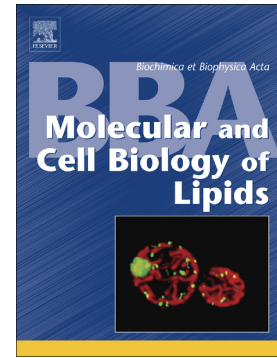
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Specialized ER Membrane Domains for Lipid Metabolism and Transport

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Abbreviations:

ATG, autophagy-related; CDS, CDP-diacylglycerol synthase; CEPT, choline/ethanolaminephosphotransferase; CPT, cholinephosphotransferase; EPT, ethanolaminephosphotransferase; ER, endoplasmic reticulum; ERMES, ER–mitochondria encounter structure; E-Syt, extended synaptotagmin; LTP, lipid transfer protein; MAM, mitochondria-associated membranes; NE, nuclear envelope; OSBP, oxysterol binding protein; ORP, oxysterol-binding protein related protein; OSH, oxysterol-binding protein homology; PM, plasma membrane; PAM, PM-associated membranes; PEMT, phosphatidylethanolamine N-methyltransferase; PI, phosphatidylinositol; PIS, phosphatidylinositol synthase; PITP, phosphatidylinositol transfer protein; PI4P, phosphatidylinositol 4-phosphate; PI(4,5)P$_2$, phosphatidylinositol 4,5-bisphosphate; PIP5K, phosphatidylinositol 4-phosphate 5-kinase; PLC, phospholipase C; PSS, phosphatidylserine synthase; SMP, synaptotagmin, mitochondrial and lipid binding protein; StAR, steroidogenic acute regulatory protein; START, steroidogenic acute regulatory (StAR) protein-related lipid transfer; VPS, vacuolar protein sorting.

ABSTRACT

The endoplasmic reticulum (ER) is a highly organized organelle that performs vital functions including *de novo* membrane lipid synthesis and transport. Accordingly, numerous lipid biosynthesis enzymes are localized in the ER membrane. However, it is now evident that lipid metabolism is sub-compartmentalized within the ER and that lipid biosynthetic enzymes engage with lipid transfer proteins (LTPs) to rapidly shuttle newly synthesized lipids from the ER to other organelles. As such, intimate relationships between lipid metabolism and lipid transfer pathways exist within the ER network. Notably, certain LTPs enhance the activities of lipid metabolizing enzymes; likewise, lipid metabolism can ensure the specificity of LTP transfer/exchange reactions. Yet, our understanding of these mutual relationships is still emerging. Here, we highlight past and recent key findings on specialized ER membrane domains involved in efficient lipid metabolism and transport and consider unresolved issues in the field. This article is part of a Special Issue entitled: ER Platforms for Membrane Lipid Dynamics edited by Shamshad Cockcroft and Christopher J. Stefan.

1. Introduction

The endoplasmic reticulum (ER) is a vast membrane compartment that extends from the nuclear envelope (NE) to cytoplasmic ER sheets and peripheral ER tubules [1]. While the ER network is continuous, it is arranged into distinct morphological and functional domains. Historically, ER sheets and tubules have been described as ribosome-studded rough ER and ribosome-free smooth ER, respectively [2, 3]. The rough ER has dedicated roles in protein translocation, quality control, and secretion. In contrast, vital functions for the smooth ER are quite diverse including calcium homeostasis [4] as well as the metabolism of membrane lipids [5], steroid hormones, and even toxic substances [6, 7]. To carry out these essential activities as needed, smooth ER cisternae and tubules are continuously formed and remodeled. Accordingly, an elegant electron tomography study has revealed a complex meshwork of peripheral ER cisternae and tubules in budding yeast cells [8]. Another recent study using super-resolution microscopy on mammalian cells has suggested that cortical ER structures that are closely apposed to the PM consist of packed ER tubules that form a dense matrix [9]. Thus, the ER consists of a diverse membrane network where specialized functions are partitioned into different structural regions.

In addition to a variety of shapes, the ER forms an elaborate system of interactions with other organelles termed membrane contact sites [10-15]. A growing number of studies have described important roles for membrane contact sites including lipid exchange and transfer [16-19]. Contact sites are thought to provide an optimal environment for non-vesicular lipid transport by maintaining a short distance (less than 30 nm) between different organelle compartments. Moreover, as first shown in seminal biochemical experiments, ER membranes associated with other compartments, such as mitochondria and the plasma membrane, are highly enriched in their capacity to synthesize phospholipids and sterols [20-23]. Taken together, these findings indicate that lipid metabolism and transport are closely coupled at ER-organelle contact sites. Here we review key discoveries and recent findings on how the ER membrane is organized to achieve efficient lipid metabolism and non-vesicular transport and how these two processes undergo mutual cross talk to promote one another.

2. Compartmentalization of phospholipid biosynthesizing enzymes in the ER

It is well known that most phospholipids are synthesized in the ER [5] (Fig. 1). However, pioneering cell fractionation experiments suggested that lipid synthesis is enriched at specialized ER subdomains associated with other organelles such as mitochondria. Accordingly, with advances in live cell imaging techniques, a heterogeneous distribution of

phospholipid biosynthesizing enzymes (but not all) within the ER has recently emerged. In many cases, this occurs at membrane contact sites where lipid transfer proteins can deliver newly synthesized lipids to other organelles for membrane expansion and homeostasis (Fig. 2). In this section, we highlight examples of phospholipid biosynthetic activities that display enriched activity within subdomains of the ER.

2.1. Phosphatidylserine (PS) synthase

One of the first studies providing compelling evidence for compartmentalization of phospholipid biosynthesis within the ER was performed by Dr. Jean E. Vance [20]. A microsomal ER fraction associated with mitochondria (called MAM, mitochondrial-associated ER membranes) purified from rat liver showed high activity for phosphatidylserine (PS), phosphatidylethanolamine (PE), and phosphatidylcholine (PC) synthesis from serine [20] (Figs. 1 and 2). Contacts between the ER and mitochondria were first observed in hepatocytes by electron microscopy in 1952 by Bernhard and colleagues [24]. A few years later, Bernhard and Rouiller speculated that ER-mitochondrial contacts might have vital roles in ER physiology [25]. However, a clearly defined role for this association remained elusive until Vance's biochemical studies decades later, revealing that ER-mitochondrial contacts are enriched in phospholipid biosynthetic activities (Figs. 1 and 2). Among them, the synthesis of PS at MAMs has been extensively analyzed [11]. In mammals, PS is synthesized by a base-exchange reaction from PC by PSS-1 or PE by PSS-2 (Fig. 1). Both PSS-1 and PSS-2 are enriched in the MAM fraction [21]. Activity of the yeast PS synthase, the Cho1 protein that generates PS from CDP-diacylglycerol (Fig. 1), is also enriched in MAM fractions [23]. Thus, an enrichment of PS synthase activity in MAM fractions is conserved in yeast and mammals in spite of the fact that PS is generated via different catalytic mechanisms in these species (Figs. 1 and 2). In yeast, PS synthase activity is also enriched in ER fractions associated with the plasma membrane (PM) called PAM, PM-associated ER membranes [22]. Based on these evidences, PS synthase activity is enriched at ER-mitochondria contacts and also at ER-PM contacts (Fig. 2). Robust PS synthase activity at membrane contact sites is likely to be supported by PS transfer proteins that function at these sites, as PS synthase is subject to product feedback inhibition in the ER (discussed in greater detail in Sections 3 and 4 below).

2.2. Cholinephosphotransferase (CPT) and ethanolaminephosphotransferase (EPT)

Most eukaryotic cells synthesize PC and PE via the CDP-choline and CDP-

ethanolamine pathways by cholinephosphotransferase (CPT) and ethanolaminephosphotransferase (EPT), respectively (Fig. 1). Biochemical fractionation analyses have shown that both CPT and EPT activities are detected mainly in microsomal ER fractions isolated from rat liver [26, 27]. In mammals, the CPT and EPT reactions are also catalyzed by CEPT1, a dual specificity choline/ethanolaminephosphotransferase [28] that is localized to the ER [29]. Interestingly, enrichment of CEPT1 at the tips of growing ER tubules in COS-7 has been reported [30]. Thus, *do novo* phospholipid synthesis via CEPT1 may drive the dynamic organization of the reticular ER network.

2.3. *Phosphatidylethanolamine N-methyltransferase (PEMT)*

Conversion of PE to PC is catalyzed by the enzyme PEMT (PE methyltransferase) in hepatocytes and by Cho2 and Opi3 in yeast via a process known as the methylation pathway (Fig. 1). PEMT activity is enriched in MAM fractions isolated from rat liver and PEMT appears to localize to MAM domains by microscopic analysis in sections from rat liver tissue [31]. In yeast cells, the majority of PC is generated by PEMTs [5]. Yeast PEMT enzymatic activities (carried out by the Cho2 and Opi3 proteins) are also readily detected in MAM fractions, while the proteins themselves may not be necessarily enriched at MAMs [23]. Another study reported that Opi3 is localized at peripheral ER structures associated with the PM where it may convert PE to PC *in trans* [32].

2.4. *Phosphatidylinositol (PI) synthase*

Phosphatidylinositol (PI) is generated from CDP-diacylglycerol by PI synthase (PIS) (Fig. 1). The site of PI synthesis has been under debate for a long time. Biochemical analyses have shown that PIS activity is found mainly in microsomal ER fractions derived from rat liver [33, 34], while PM fractions were also reported to have high PIS activity under different experimental conditions [35, 36]. In addition, PIS activity has also been detected in Golgi compartment fractions derived from rat liver and yeast [26, 37]. A study has even suggested that PIS is enriched in highly mobile ER-derived compartments in intact COS-7 cells [38]. These mobile PIS compartments transiently contact other organelle membranes [38]. Another study has shown that PIS-enriched assemblies are mainly formed at the leading edge of dynamic ER tubules in COS-7 cells. These structures also contain the phospholipid biosynthesizing enzyme CEPT1 (Fig. 1) [30]. Similar PIS assemblies in the ER have been confirmed in other cell lines (HeLa and RPE cells) [39, 40] suggesting that PIS is most likely present in specialized ER subdomains. Given that PIS activity is enriched in MAM and PAM

fractions derived from yeast cells [22, 23], the punctate PIS structures could reflect localization at membrane contact sites between the ER and other compartments. Localization to PAM fractions may play an important role in the synthesis of phosphoinositide lipids at the PM, as discussed by other review articles by the Balla and Cockcroft groups in this issue [41, 42].

The involvement of PIS-enriched domains in autophagosome formation has been also reported [43]. Under starvation conditions, various autophagy-related (ATG) proteins are sequentially recruited to the ER membrane to induce autophagosome formation in mammalian cells. In spite of the fact that ATG proteins associate with the ER membrane at an early stage of autophagy, they do not show a typical reticular ER distribution. Instead they form a punctate structure at the ER, implying the existence of an ER subdomain required for autopahgosome formation. Interestingly, the ATG protein assemblies are recruited to a PIS-enriched ER subdomain to initiate autophagosome formation [43]. As phosphatidylinositol 3-phosphate (PI3P) formation is a critical step for autophagosome formation, the PIS-enriched domain might be involved in PI3P metabolism at ER-isolation membrane contact sites [44].

3. Phospholipid transfer between the ER and other compartments by lipid transfer proteins (LTPs)

Newly synthesized lipids in the ER are delivered to their final destination via vesicular and non-vesicular mechanisms (see a review article by Drs. Funato, Riezman and Muñiz in this issue) [45]. However, bulk lipid transport is thought to occur in a non-vesicular fashion via lipid transfer proteins (LTPs). In general, LTPs have cytoplasmic domains bearing hydrophobic cavities that extract and exchange lipid molecules between membranes. Many proteins belong to lipid transfer protein families based on sequence homology; however which LTPs transport which lipids *in vivo* has been less clear. Several recent studies have revealed physiological ligands of LTPs and proposed models for lipid exchange and transport. In this section, we briefly summarize recent progress on phospholipid transfer proteins. Several other excellent reviews provide a comprehensive review of LTPs and transport of other lipids including sterols [16, 18, 46].

3.1. Class I PITPs

The first phosphatidylinositol transfer protein (PITP) was purified from bovine brain and shown to bind, exchange, and transfer phospholipids *in vitro*, in particular PI and PC [47]. In mammals, there are five PITP proteins that are categorized into Class I and II based on

sequence differences [48]. Class I PITPs (PITPα and PITPβ) consist only of a PITP domain and have dual ligand binding specificity for PI and PC [47, 49]. Accordingly, PITPα and PITPβ efficiently transfer PI or PC between membranes *in vitro* [50]. The crystal structures of PITPα and PITPβ reveal a hydrophobic pocket that can accommodate a single phospholipid molecule, either PI or PC [51-54]. Structural analysis of PITPα bound to PI has shown that four residues (Thr-59, Lys-61, Glu-86 and Asn-90) are critical for PI binding, but not PC binding [52]. In contrast, the Cys-95 residue in the head group binding pocket of PITPβ is required for PC binding [55]. Given that these residues are conserved in both PITPα and PITPβ [52, 55], it is proposed that PI/PC exchange or transfer is the common function of Class I PITPs. In one model, it has been suggested that PITPβ transfers PI from the ER to the cis-Golgi compartments to facilitate phosphatidylinositol 4-phosphate (PI4P) synthesis by PI 4-kinase [55]. At ER-PM contacts (PAM), PI exchange or transfer by Class I PITPs has been implicated in phospholipase C and EGF receptor signaling by promoting phosphoinositide kinase activities [56, 57]. However, strong arguments have proposed that Class I PITP lipid exchange activity (rather than lipid transfer *per se*) suffices for PI 4-kinase activity *in vivo* [58]. Thus, whether Class I PITPs function as PI transfer proteins or as PI exchange proteins *in vivo* remains an issue that is currently still under debate.

3.2. Class II PITPs

Class II PITPs include PITPNM1/RdgBαI/Nir2, PITPNM2/RdgBαII/Nir3 and PITPNC1/RdgBβ. The name RdgB is derived from retinal degeneration type B describing the phenotype manifested in *Drosophila* lacking a functional RdgBα protein [59]. Mammalian RdgBαI/Nir2 (Class II), but not mammalian PITPα (Class I), rescues the fly RdgBα mutant indicating that Class I and II PITPs are functionally different [60]. A recent study has shown that, unlike Class I PITPs, Class II PITPs have the ability to bind phosphatidic acid, PA, instead of PC [61]. Consistent with this observation, Cys-95, a key residue for PC binding in PITPβ, is replaced with threonine in Class II PITPs [61]. Thus, Class II PITPs mainly exchange or transfer PI and PA, not PC. As such, Class II PITPs serve as key factors at ER-PM contacts (PAM) during phospholipase C signaling and the phosphoinositide cycle (see two review articles by the Balla and Cockcroft groups in this issue) [41, 42]. Indeed, several studies have shown that Class II PITPs (Nir2, Nir3 and Drosophila RdgBα) enhance phosphatidylinositol 4,5-bisphosphate, $PI(4,5)P_2$, re-synthesis by exchanging PI/PA at ER-PM contact sites *in vivo* [62-66].

3.3. Sec14/CRAL-TRIO domain family

Sec14 is the prototype of the Sec14 domain (also referred to as the CRAL-TRIO domain) superfamily, as it was first characterized as a PI/PC exchange protein essential for Golgi secretory function and cell viability in yeast [67-70]. Yeast mutant cells lacking Sec14 function can be rescued by overexpression of mammalian PITPs [71, 72]. Moreover, Sec14 and mammalian Class I PITPs show a common function for PI/PC exchange in permeabilized cells [73] in spite of the fact that Sec14 has no sequence or structural homology to mammalian PITPs. Based on genetic and biochemical evidence [74-76], it is proposed that Sec14 coordinates PC and PI4P metabolic pathways with Golgi network organization and function. Crystal structures of Sec14 and Sfh1 (the closest Sec14 homolog) demonstrate that the Sec14/CRAL-TRIO domain forms a hydrophobic pocket that is occupied by one phospholipid molecule [77-79]. Both PI and PC binding activities of Sec14 are essential for cell growth and stimulation of PI4P synthesis in yeast [77]. Curiously, some mammalian Sec14-related proteins bind other hydrophobic ligands such as 11-*cis*-retinol, α-tocopherol, or squalene with high affinity rather than PI *in vitro* [80]. While it is unclear whether all mammalian Sec14 family members carry out phospholipid exchange, the Sec14-like domain of neurofibromin/NF1 can harbor a phospholipid molecule *in vitro* [80-82]. Future studies are needed to determine whether mammalian Sec14-like isoforms have a conserved role in the control of PI4P synthesis as PI exchange proteins.

3.4.1. ORP/Osh protein family

O̲xy̲sterol b̲inding p̲rotein (OSBP) was originally identified as a cytosolic protein that strongly binds 25-hydroxycholesterol [83, 84]. Based on sequence homology, >12 O̲SBP-r̲elated p̲roteins (encoded by the OSBP and ORP1-11 genes) in humans and 7 O̲SBP h̲omology (Osh: Osh1-7) proteins in yeast have been found [85]. Although physiological ligands of ORP/Osh proteins had been somewhat mysterious [86-96], structures of Osh protein-lipid complexes have provided important insight into their functions as sterol and phosphatidylserine (PS) exchange and transfer proteins *in vitro* and *in vivo* [97-103]. Importantly, while some ORP/Osh proteins bind to sterol lipids and other family members bind PS, they are all capable of binding PI4P [104, 105]. The PI4P headgroup interacts with residues that are highly conserved in ORP/Osh proteins, suggesting that PI4P is a common

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ligand of ORP/Osh proteins [104, 105]. Thus, it has been proposed that ORP/Osh proteins exchange PI4P for other lipid molecules. Specifically, OSBP [106] and Osh4 [107] are proposed to serve as sterol/PI4P exchange proteins in the early secretory pathway and ORP5/8 in mammals and Osh6/7 in yeast function as PS/PI4P exchange proteins at ER-PM contact sites (PAM) in the control of PI4P and PS levels at the PM [108, 109]. Based on these findings, an elegant 'counter current' model has been proposed whereby ORP/Osh proteins transfer PS or sterol against their gradients in exchange for PI4P at the target membrane [110, 111]. In line with this idea, additional ORP/Osh proteins show dual sterol/PI4P binding [112-114].

3.4.2. Must ORP/Osh proteins use counter currents?

The counter current model for ORP/Osh protein function poses that a newly synthesized sterol or PS molecule is selectively removed from the ER and delivered to a target membrane organelle in exchange for PI4P continuously synthesized at that site. It is proposed that the PI4P-bound ORP/Osh protein must return to the ER where it releases PI4P for hydrolysis by an ER-localized phosphatase named Sac1. This elegant model is illustrated in detail by recent *in vitro* studies [107, 109]. However, while ORP/Osh function is essential in all eukaryotic cells, work in yeast and mammalian cells has shown that Sac1 activity in the ER is not an obligate requirement [115-117]. Even though cells require Sac1 activity for viability [115, 118, 119], this activity may occur elsewhere than the ER (Golgi compartments, endosomes, and even the cytoplasm). This is likely because cells express other Sac1-like activities (such as the synaptojanins and even Sac2 in mammalian cells) that localize to other compartments in the cell including transport vesicles, Golgi compartments, and endosomes. As such, ORP/Osh proteins may present PI4P to Sac1 domain-containing phosphatases at target membranes where these enzymes reside.

Why might subtle distinctions in the 'counter current' model be important? First of all, they could afford a net gain (+1) of lipid, as the target membrane may retain the PI molecule. This may be especially important for membrane expansion during *de novo* biogenesis of a membrane compartment (*i.e.* peroxisomes and autophagosomes) or for transport vesicles undergoing directed transport that undergo fission/fusion reactions and mature *en route* to their final destination. In addition, PI4P-independent and Sac1-independent ORP/Osh protein function has been demonstrated *in vitro* and *in vivo* [107, 117]. Moreover, $PI(4,5)P_2$ has been suggested to be a ligand for ORP proteins *in vitro*, and sterol/$PI(4,5)P_2$ exchange has been proposed for mammalian ORP family members *in vivo*

[120-122]. The involvement of ORP5 and ORP8 in mitochondrial function has been also reported [123]. Whether PI4P is synthesized at mitochondria and is needed for ORP5/8 function at mitochondria remains unclear. Thus, alternative modes for ORP/Osh protein function may exist *in vivo*.

3.5. The START domain family

The steroidogenic acute regulatory protein (StAR)-related lipid transfer (START) domain family shares a unique structural module for harboring lipids, named as the START domain [124]. The START domain structure bears a hydrophobic pocket that can accommodate one lipid molecule [125-130]. In humans, the START domain family consists of 15 proteins that fall into six subgroups based on sequence and ligand-binding similarities. The STARD1/D3 subgroup and STARD4/D5/D6 subgroup commonly bind cholesterol *in vitro*. The founding member of START domain family members, STARD1/StAR is essential for cholesterol transport from the outer to the inner mitochondrial membrane to initiate steroid hormone biosynthesis in adrenal and gonad tissues [131]. STARD3/MLN64 is ubiquitously expressed and involved in cholesterol transport at ER-endosome contact sites [132]. STARD4, STARD5 and STARD6 are composed of only a START domain that binds cholesterol, bile acids, or steroids *in vitro* [133, 134]. In contrast, the STARD2/D7/D10/D11 subgroup members, STARD2, STARD7 and STARD10 bind PC *in vitro* [125, 135, 136]. Notably, STARD7 maintains mitochondrial PC composition by transferring PC *in vivo* [137-139]. STARD11/CERT has been well characterized as a ceramide transfer protein [140]. STARD11/CERT transfers ceramide from the ER to the *trans*-Golgi apparatus where it is converted to sphingomyelin. Interestingly, STARD11/CERT weakly binds diacylglycerol *in vitro* [127]. Diacylglycerol is produced by conversion of ceramide to sphingomyelin. Therefore, a model of ceramide/diacylglycerol exchange by STARD11/CERT has been proposed [18]. Diacylglycerol may be transferred back to the ER by STARD11/CERT to be utilized for further rounds of lipid synthesis.

3.6. SMP protein family

The SMP (synaptotagmin, mitochondrial and lipid binding protein) domain has been recently characterized as a lipid-harboring and transfer module. The SMP domain of Extended-Synaptotagmin 2 (E-Syt2) has been shown to dimerize forming an extended hydrophobic tube that preferentially binds glycerolipids [141], consistent with bioinformatic predictions [142, 143]. As E-Syt isoforms and the yeast ortholog tricalbin proteins localize to

ER-PM contact sites [144-146], their roles in lipid transfer between ER and the PM are expected. In fact, E-Syt proteins can transfer phospholipids and diacylglycerol between membrane bilayers with little or no headgroup specificity *in vitro*. The transfer is concentration gradient-dependent and Ca^{2+}-dependent however [147, 148]. In a physiological context, it has been proposed that E-Syts transfer excess diacylglycerol from the PM to the ER after $PI(4,5)P_2$ hydrolysis by PLC [147]. Another SMP containing protein, TMEM24 (also known as C2CD2L), concentrates at ER-PM contact sites and transfers phospholipids, with a preference for PI, to the PM in response to PLC signaling [149].

A SMP domain is also found in the ERMES (ER-mitochondrial encounter structure) complex components Mdm12, Mmm1 and Mdm34. The ERMES complex was originally identified as a tethering complex that maintains ER-mitochondria contact sites in yeast [150]. As the conversion of PS to PC is impaired in ERMES mutants and because mitochondria can synthesize PE, a role for the ERMES complex in phospholipid exchange between the ER and mitochondria has been proposed. The overall backbone structures of Mdm12 and Mmm1 resemble that of the SMP domain of E-Syt2, including the presence of hydrophobic cavities and an ability to bind phospholipids *in vitro* [151-153]. Accordingly, the isolated Mmm1-Mdm12 complex carries out efficient phospholipid transfer between liposomes *in vitro* [154]. Thus the ERMES complex may mediate phospholipid transfer between the ER and mitochondria *in vivo*. Further analyses are needed to fully understand the role of ERMES complex in lipid transfer and metabolism *in vivo*.

3.7. Vps13 and Atg2

The Vps13 protein family is highly conserved in eukaryotes. Yeast has a single *VPS13* gene, while the human genome contains four VPS13 genes (VPS13A-D). Mutations or perturbations in the expression of VPS13 genes are associated with various human disorders [155]. Yet despite their known importance, a molecular function for Vps13 family members had been unclear for quite some time. However, an unbiased and comprehensive genetic study revealed that the growth defect of yeast ERMES mutants can be bypassed by fortuitous gain-of-function mutations in the *VPS13* gene [156]. Consequently, it was found that yeast Vps13 localizes to membrane contact sites between various organelles including ER-mitochondrial contacts [156, 157]. This led to the notion that Vps13 proteins might be involved in lipid transfer, and work by the De Camilli and Reinisch groups have recently shown that the N-terminal portion of Vps13 is tubular with a hydrophobic cavity that can accommodate a large number of lipids. This region of Vps13 efficiently transfers

glycerolipids between liposomes *in vitro* [158]. Interestingly, the N-terminal portion of Vps13 is similar to the N-terminus of the Atg2 protein [159], implying that Atg2 may transfer lipids as well. Indeed, the crystal structure of the N-terminus of Atg2 has been recently resolved and its phospholipid transfer activity has been demonstrated *in vitro* [160, 161]. Surprisingly, a Vps13-Atg2 chimera in which the N-terminus of Atg2 is replaced with the N-terminus of Vps13 almost fully rescued impaired autophagic activity in *atg2Δ* mutant yeast cells. These results indicate that the N-terminus of Vps13 and Atg2 share a key function in transferring phospholipids [160]. As the Vps13 and Atg2 N-terminal regions have no similarity to any characterized lipid transfer module, they are a novel type of LTP.

4. Relationships between phospholipid metabolism and non-vesicular lipid transfer

As described above, some phospholipid biosynthesis enzymes are enriched at ER membrane subdomains. Similarly, some LTPs efficiently target to ER subdomains often corresponding to membrane contact sites where they transfer/exchange lipids between different organelle membranes. The similarities in their distribution imply functional relationships. Next we review recent findings regarding these close connections and discuss possible molecular mechanisms linking phospholipid metabolism and transport.

4.1. LTPs enhance the activity of phospholipid metabolizing enzymes

LTPs may promote lipid metabolism by various mechanisms (Fig. 3). A simple mechanism is to increase substrate concentration. As such, LTPs may stimulate lipid metabolism by supplying substrates to the membrane domain where enzymes localize (Figs. 3A and 3B). For example, it is thought that PITPs including Nir2 and TMEM24 stimulate PM-localized PI kinase activity by transferring PI from the ER to the PM [48, 65, 66, 149]. The Class II PITP Nir2 is also proposed to transfer PA from the PM to the ER where the ER-localized CDS and PIS enzymes convert it to PI. Another mechanism by which LTPs may facilitate lipid metabolism is substrate presentation. As some enzymes cannot efficiently use a lipid substrate within a lipid bilayer, LTPs may extract and present a lipid to an enzyme in order to stimulate its enzymatic reaction (Fig. 3C). This model has been proposed for the Sec14 protein [75, 77] whereby Sec14-mediated PI/PC exchange promotes interfacial presentation of PI to PI 4-kinase to generate PI4P. Based on *in vitro* results, ORP/Osh proteins have similarly been suggested to present PI4P to the Sac1 phosphatase [162], but further studies are needed to determine whether this occurs *in vivo*. As some lipid metabolizing enzymes are

activated by lipids other than a substrate [163], LTPs might also enhance enzymatic activities by delivering a stimulatory lipid (Fig. 3D). In line with this model, we have recently reported that PS and sterol supplied by Osh proteins allosterically activate PI(4,5)P$_2$ synthesis by PIP5K [164], which in turn ensures PM organization and integrity [164, 165]. On the other hand, some lipid metabolizing enzymes undergo product feedback inhibition [166, 167]. Therefore, LTPs might be needed to remove an inhibitory lipid from the membrane where enzymes are working to maintain their high enzymatic activity (Fig. 3E). A prime example is found in PS synthases (mammalian and yeast) that are inhibited by PS in the ER (product feedback inhibition) and the ORP/Osh proteins that transfer newly synthesized PS from the ER (ORP5/8 and Osh6/7). Thus, ORP/Osh protein-mediated PS transfer may sustain PS synthesis in the ER and stimulate PS-dependent activities at the PM (such as protein kinases, PIP5K, and Rho-family small GTPases) [164, 168, 169]. Indeed, inactivation of the yeast Osh proteins leads to a significant reduction in cellular PS levels as well as decreased PS in the cytoplasmic leaflet of the PM [164].

4.2. Phospholipid synthesis facilitates loading of lipid molecules to LTPs.

Are there other reasons why phospholipid biosynthesis enzymes are compartmentalized within the ER? Several studies have proposed that enrichment of phospholipid biosynthesis enzymes might facilitate non-vesicular lipid transfer at membrane contact sites (Figs. 4 and 5). In 1991, Dr. Jean E. Vance reported that newly synthesized PS and PE are efficiently transferred between ER microsomes and mitochondria isolated from rat liver [170]. Similarly, another group has shown that newly synthesized PS is rapidly translocated from the ER to the mitochondria and metabolized into PE in permeabilized yeast cells [171]. A more recent study has directly demonstrated the stimulatory effect of localized PS synthesis on lipid transfer activity. Artificially targeting *E. coli* PS synthase, a peripheral membrane protein that has no homology to yeast or mammalian PS synthases, to ER-mitochondria contacts (MAM) promotes PS transport from the ER membrane to mitochondria in yeast [166].

How does phospholipid synthesis enhance non-vesicular lipid exchange and transfer? Lipid transport by LTPs is divided into several different steps (Fig. 2). First, LTPs must dock to donor membranes and load a lipid ligand (Steps 1-3 in Fig. 2). One possibility is that localized enrichment of lipid biosynthesis enzymes can increase the local concentration of lipid ligands. This may be especially important, given that lipids can be flipped to the luminal side of the ER membrane (by either spontaneous or flippase-induced transbilayer

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movements) thereby effectively reducing their amounts on the cytoplasmic leaflet. Compartmentalized lipid biosynthesis within ER subdomains may establish localized concentration gradients of newly synthesized lipids for LTP capture (Fig. 4A and 4B). As phospholipid remodeling mainly occurs in the ER membranes, we also have to consider changes in fatty acid composition of ER phospholipids. The fatty acid composition of nascent lipids might be preferred by LTPs compared to lipids with prolonged ER retention times that are more likely to have undergone acyl chain remodeling (Fig. 4C). In support of this idea, the Osh6 protein preferentially transfers saturated *PS in vitro* [109]. It will be important to examine whether alterations in phospholipid remodeling pathways affect lipid exchange and transfer *in vivo*. Another possibility is a regulatory effect of lipid metabolism on LTP functions. Lipid metabolizing enzymes might generate stimulatory lipids (Fig. 4D) or consume some inhibitory lipids for LTP docking/loading steps (Fig. 4E). Indeed, given that PI3P stimulates Atg2-dependent lipid transfer *in vitro* [160], it is reasonable to consider that PI3P synthesis might enhance Atg2-dependent lipid transfer *in vivo*. In addition, at least two studies have proposed a key role for ER-shaping factors in phospholipid metabolism and LTP function [30, 172]. Phospholipid metabolic enzymes and LTPs might share similar preferences for membrane curvature such as ER tubules (Fig. 4F).

4.3. Phospholipid metabolism and unloading of lipid molecules from LTPs

After lipid ligand loading, LTPs target and dock to acceptor membranes and then unload the ligand (Steps 5-7 in Fig. 2). As lipid metabolism may consume a lipid ligand and reduce its local concentration, this may effectively prevent re-extraction of the transferred lipid and thus promote directional transfer (Figs. 5A and 5B). Likewise, some enzymes may generate a competitive ligand for LTPs and facilitate an exchange of lipid ligands in the same membrane (Fig. 5C). A good example is Class II PITPs. After Nir2 and Drosophila RdgBα transfer PA to the ER, the PA is converted into PI by CDS and PIS in the ER membrane (ligand consumption, Fig. 5B). As newly synthesized PI is also a ligand for Class II PITPs with a higher affinity compared to PA [66], PA is released and instead PI is loaded (competitor ligand, Fig. 5C). Another example is ORP5/8 in mammals and Osh6/7 in yeast. These ORP/Osh proteins extract PI4P from the PM and bring it back toward the ER for hydrolysis by Sac1 in the ER membrane (ligand consumption, Fig. 5B). The ORP proteins then in turn extract newly synthesized PS in the ER (competitor ligand, Fig. 5C). Although the binding affinity of PS to ORP proteins is less than that of PI4P [109], the concentration of

PI4P is thought to be extremely low in the ER due to Sac1. Alternatively, it is also possible that lipid metabolism generates some stimulatory lipids for unloading ligands (Fig. 5D). For example, PI(4,5)P_2 is thought to stimulate sterol release from Osh proteins [99, 173] and STARD family members [174].

5. Future questions

Although the significance of ER subdomains in lipid metabolism and transport was first proposed almost 30 years ago, the past few years have seen tremendous advances in our knowledge of lipid dynamics. Recent studies have identified physiological ligands of LTPs and presented insightful models for non-vesicular lipid transport machinery. In particular, structural analyses have facilitated a better understanding of how LTPs harbor and transfer lipids. Of note, some LTPs such as the E-Syt, Vps13, and Atg2 proteins not only serve as lipid carriers but also as tethers that form ER-organelle contact sites *in vivo*, further suggesting that lipid exchange and transfer events are coupled with membrane contact site formation. While these advances have pushed the field forward, many key issues remain to be clarified. How the directionality of lipid exchange and transfer is regulated is still a big mystery in this field. Some LTPs move lipids from high to low concentration, while other LTPs transfer them against their concentration gradients *in vivo*. Thus another major question involves how various LTPs activities are coordinated to result in net membrane lipid gain or changes in membrane lipid composition as needed. An additional point is that *in vitro* lipid transport by LTPs is not as high as predicted *in vivo*. It has been argued that there is a big gap between *in vitro* lipid transport rates and lipid demand *in vivo* [175-177]. These discrepancies might be explained by the contribution of yet uncharacterized factors in the loading/unloading steps of LTPs. Possibly, lipid inter-conversion and metabolism may play important roles in the rapid transfer rates observed *in vivo*. To address this issue, novel methods to detect and evaluate lipid movements *in vivo* are needed. Finally, unlike typical LTPs, some SMP domain proteins, Vps13 family, and Atg2 family members have a capacity to bind multiple lipids with little or no headgroup specificity *in vitro*. Therefore, it is natural to consider that these proteins need to be coupled with lipid metabolism enzymes to achieve selective lipid transport *in vivo*. Important questions in lipid metabolism and transport will undoubtedly continue to be a major focus of cell biology research.

Conflict of interest

The authors declare no competing financial interests.

Acknowledgements

Figure Legends

Figure 1. Phospholipid biosynthesis pathways

Phospholipid biosynthesis pathways in yeast and mammalian cells. Yeast-specific, mammalian-specific, and common pathways are shown in blue, red and black lines respectively. PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; PI, phosphatidylinositol; PG, phosphatidylglycerol; PA, phosphatidic acid; lysoPA, lysophosphatidic acid; DAG, diacylglycerol; TAG, triacylglycerol; CDP-DAG, cytidine diphosphate-diacylglycerol; GPAT, glycerol-3-phosphate acyltransferase; LPAAT, lysoPA acyltransferase; PAP, phosphatidate phosphatase; DGAT, acyl-CoA:diacylglycerol acyltransferase; CDS, CDP-DAG synthase; PIS, phosphatidylinositol synthase; PSS, phosphatidylserine synthase; PSD, phosphatidylserine decarboxylase; PEMT, phosphatidylethanolamine N-methyltransferase; P-Ch, phosphocholine; P-Et, phosphoethanolamine; CDP-Ch, CDP-choline; CDP-Et, CDP-ethanolamine; CPT, cholinephosphotransferase; EPT, ethanolaminephosphotransferase; CEPT, choline/ethanolaminephosphotransferase.

Figure 2. Non-vesicular lipid transfer by box-type LTPs

[Top panel] Sequential lipid transfer by box-type lipid transfer proteins (LTPs), such as PITPs, ORP/Osh proteins, CRAL-TRIO family members and STARD proteins, is divided into 8 distinct steps. (1) A LTP docks to a donor membrane. (2) The LTP extracts a lipid ligand from the donor membrane. (3) The LTP detaches from the donor membrane and its lid closes. (4) The LTP is targeted toward an acceptor membrane. (5) The LTP docks to the acceptor membrane. (6) The lid of the LTP opens. (7) The lipid ligand is released and transferred to the acceptor membrane. (8) The LTP detaches from the acceptor membrane.

[Bottom panel] A cartoon showing membrane contact sites in cells. The endoplasmic reticulum (ER) is associated with other organelle membranes, such as mitochondria, the plasma membrane (PM), the trans-Golgi network (TGN), endosomes (End), and lipid droplets (LD). PAM, PM-associated membranes; MAM, mitochondria-associated membranes. Please see additional review articles in this issue for more information on ER-endosome and ER-lipid droplet contacts.

Figure 3. Models for stimulation of phospholipid metabolism by LTPs

(A) Basal enzymatic conversion of a lipid substrate to a new lipid product in the absence of

lipid exchange and transfer. (B-E) LTPs can stimulate an enzyme by supplying substrates to membranes where an enzyme is localized (B), by directly presenting substrates to an enzyme (C), by delivering stimulatory lipids to membranes where an enzyme is localized (D), and by removing inhibitory lipids from membranes where an enzyme is localized (E).

Figure 4. Models for stimulation of LTP loading by phospholipid metabolism.

(A) Basal LTP lipid extraction activity in the absence of phospholipid metabolism. (B) An enzyme generates newly synthesized lipids and increases their local concentration to facilitate the loading of lipid ligands to LTPs. (C) An enzyme modifies the fatty acid compositions of ligands and increases amount of lipids containing fatty acid species preferred by LTPs as a ligand. (D) An enzyme generates stimulatory lipids and enhances membrane association of LTPs. (E) An enzyme consumes competing ligands and to facilitate loading of ligands to LTPs. (F) An enzyme and LTPs might have a similar preference for membrane curvature. Increased membrane curvature is proposed to decrease the energy barrier for lipid extraction.

Figure 5. Models for stimulation of LTP unloading by phospholipid metabolizing enzymes.

(A) Basal LTP unloading of lipid ligands to an acceptor membrane in the absence of an enzyme. (B) An enzyme consumes ligands in the acceptor membrane and reduces their local concentration, which can facilitate unloading steps of ligands from LTPs. (C) An enzyme generates competing ligands and increases their local concentration, which can prevent re-extraction of transferred ligands by LTPs. (D) An enzyme generates lipid stimulators and enhances membrane association of LTPs, which results in an enhancement of unloading step of ligands from LTPs.

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Highlights

- Lipid metabolism is sub-compartmentalized in the endoplasmic reticulum.

- The endoplasmic reticulum forms membrane contact sites with numerous organelles in the cell.

- Lipid exchange and transport are facilitated by lipid transfer protein activities at organelle contacts.

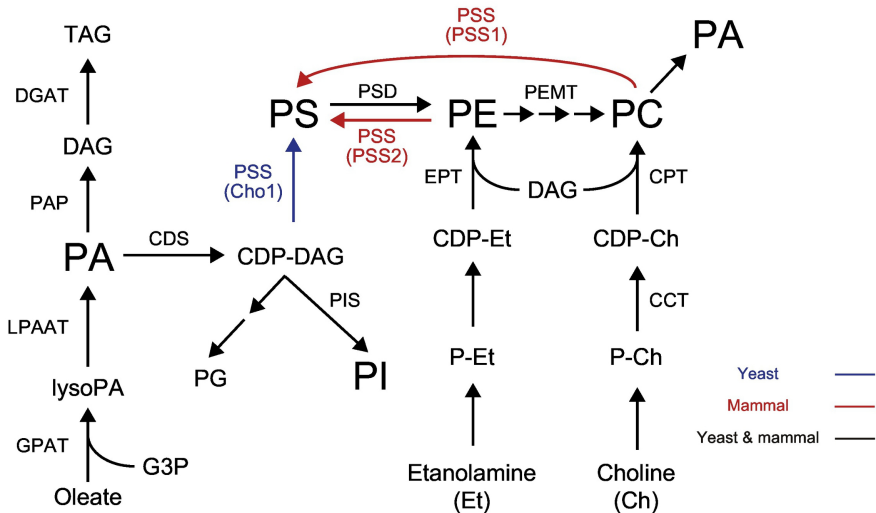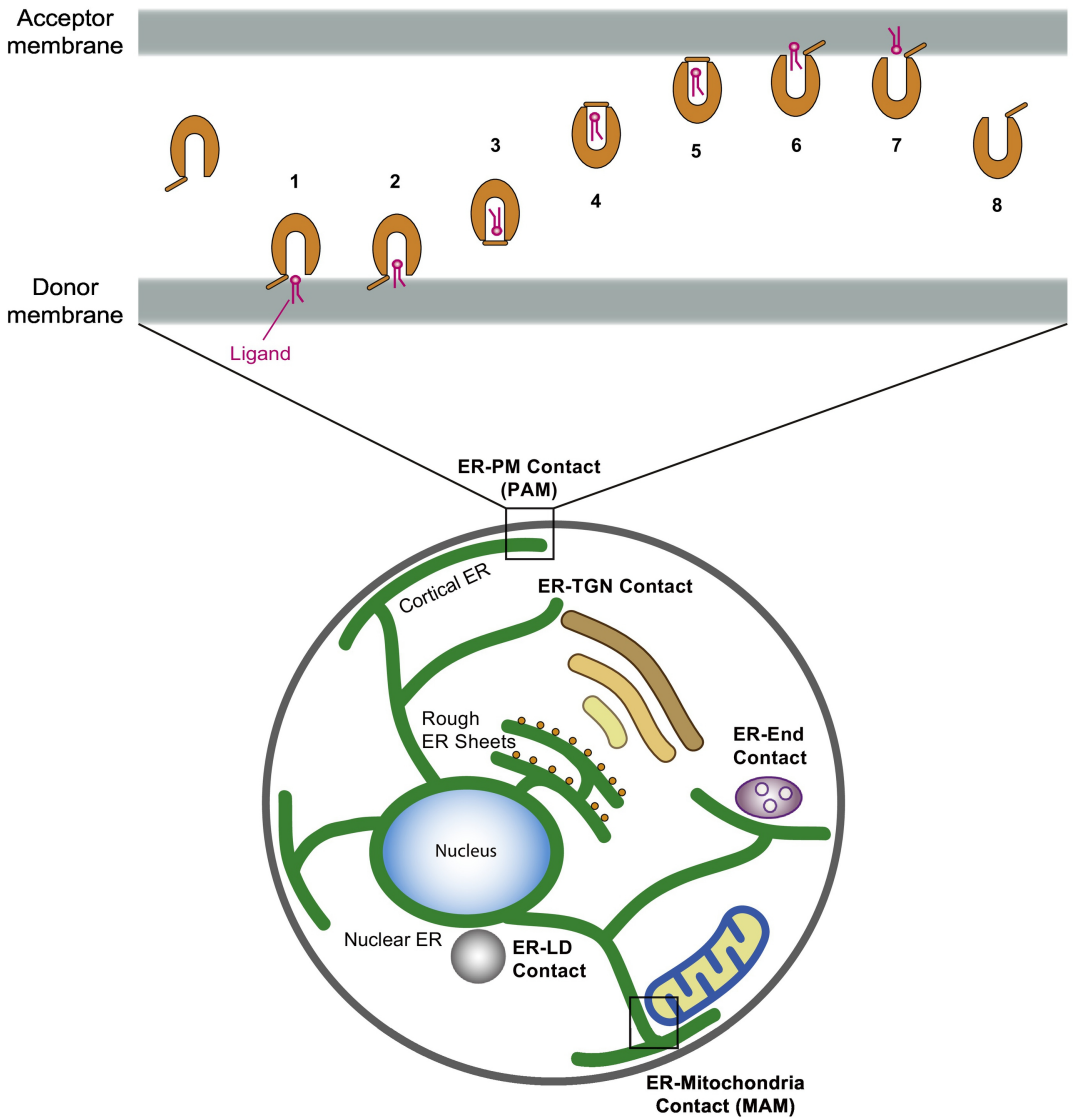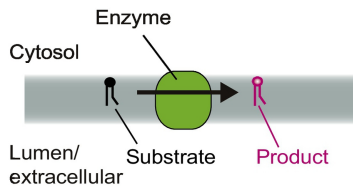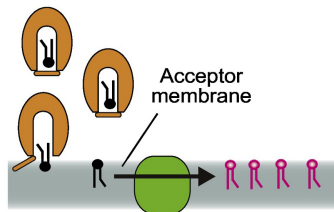- Lipid metabolism and transport pathways undergo mutual cross talk.

Figure 1

Figure 2

A

Cytosol

Enzyme

Substrate → Product

Lumen/extracellular

B Supply substrates

Acceptor membrane

C Present substrates

D Supply stimulators

Acceptor membrane

Stimulator

E Remove inhibitors

Donor membrane

Inhibitor

Figure 3

A No enzyme

Cytosol

Donor membrane

Lumen/extracellular

Pre-existing lipid

B Local enrichment

Enzyme

Newly synthesized Lipid

C Fatty acid composition

Pre-existing lipid (remodeled)

D Increase stimulators

Enzyme

Stimulator

E Reduce competitors

Competitor

F Optimal membrane shape

Figure 4

A   No enzyme

Cytosol

Acceptor membrane

Lumen/extracellular

B   Consume ligands

Enzyme

Ligand

C   Increase competitors

Competitor

D   Increase stimulators

Stimulator

Figure 5