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SMP domain proteins in membrane lipid dynamics

Darshini Jeyasimman¹ and Yasunori Saheki^{1,2}

¹Lee Kong Chian School of Medicine, Nanyang Technological University, 308232, Singapore

²Institute of Resource Development and Analysis, Kumamoto University, Kumamoto 860-0811, Japan

Correspondence: yasunori.saheki@ntu.edu.sg

Keyword

TULIP, SMP, ER, membrane contact sites, lipid transport

Abstract

Synaptotagmin-like mitochondrial-lipid-binding (SMP) domain proteins are evolutionarily conserved family of proteins in eukaryotes that localize between the endoplasmic reticulum (ER) and either plasma membrane (PM) or other organelles. They are involved in tethering of these membrane contact sites through interaction with other proteins and membrane lipids. Recent structural and biochemical studies have demonstrated that SMP domain proteins transport a wide variety of lipid species by the ability of the SMP domain to harbor lipids through its unique hydrophobic cavity. Growing evidence suggests that SMP domain proteins play critical roles in cell physiology by their actions at membrane contact sites. In this review, we summarize the functions of SMP domain proteins and their direct roles in lipid transport across different membrane compartments. We also discuss their physiological functions in organisms as well as “bypass” pathways that act in parallel with SMP domain proteins at membrane contact sites.

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1. Introduction

The endoplasmic reticulum (ER) spreads throughout the cell and forms physical contacts with virtually all other cellular organelles and the plasma membrane (PM) [1,2]. At these contacts (i.e. membrane contact sites), protein-protein and/or protein-lipid interactions mediate tethering of two closely apposed membranes (typically 10~30 nm) without inducing membrane fusion. Recent studies have identified a number of key proteins, including SMP domain proteins, that localize to these membrane contact sites and regulate their tethering and functions, such as lipid transport, organelle dynamics, Ca^{2+} homeostasis and signaling [3–10].

SMP domain proteins belong to the superfamily of TUBular LIPid-binding (TULIP) domain-containing proteins, which additionally contain the bacterial/permeability-increasing protein-like (BPI-like) family proteins and Takeout-like family proteins [11]. BPI-like and Takeout-like family proteins are extracellular proteins with various functions, ranging from immunity against bacteria to lipid transport between lipoproteins [11]. In contrast, SMP domain proteins are intracellular proteins, localizing at various membrane contact sites [12].

TULIP domains adopt cylindrical barrel-like structure with a central cavity lined with hydrophobic amino acid residues that binds to lipids and other hydrophobic ligands [11]. Indeed, structural studies revealed that the SMP domain accommodates acyl chains of glycerolipids through its central hydrophobic cavity with or without particular selectivity against their headgroup (please see below for the lipid binding preference of individual SMP domains) [13–17]. As SMP domain proteins localize to membrane contact sites, they are proposed to play major roles in shuttling lipids between the ER, other organelles, and the PM. Studies of SMP domain proteins in several organisms, in particular yeast and mammals, have contributed significantly to our understanding of the mechanisms of intracellular non-vesicular lipid transport. Here, we discuss the functions of SMP domain proteins and summarize their known roles in cell physiology.

2. SMP domain proteins at ER-PM contacts

E-Syts

Extended-synaptotagmins (E-Syts: E-Syt1, E-Syt2 and E-Syt3) (tricalbins in yeast) are evolutionarily conserved ER-PM tethering proteins that are present in all eukaryotes [18–22] (**Figure 1**).

E-Syts, anchored to ER membrane via their N-terminal hydrophobic stretch, possess a cytosolic lipid-harboring SMP domain followed by several C2 domains [18,23] (**Figure 1**). They form homo- and hetero-meric complexes and mediate ER-PM tethering via their C2 domain-dependent interaction with PM phosphoinositide $\text{PI}(4,5)\text{P}_2$ that is additionally regulated by cytosolic Ca^{2+} [18,24–26] (**Figure 1**). In particular, overexpression of E-Syt2/3 leads to massive expansion of ER-PM contacts [18,24]. The SMP domain of E-Syt2 forms a dimer of approximately 90-Å-long cylinder, containing a deep hydrophobic groove that harbors glycerolipids without particular selectivity against head groups [13] (**Figure 2a**). At most ER-PM contacts, two membranes are separated by approximately 20nm. Thus, it was proposed that the SMP dimer of E-Syts shuttles between the ER and the PM and transfer lipids, without both ends of the dimer simultaneously touching the ER membrane and the PM [3,13,23,24]. Purified E-Syt1 protein transports glycerolipids, including diacylglycerol (DAG), between liposomes via its SMP domain's ability to harbor lipids; such lipid transfer is bidirectional, driven by concentration gradient of lipids present in tethered membranes, and stimulated by 5-200 micromolar range of Ca^{2+} [27–29]. While Ca^{2+} binding to the C2C

domain of E-Syt1 triggers Ca^{2+} -regulated ER-PM tethering [18,24,25,30], Ca^{2+} binding to the C2A domain of E-Syt1 releases the autoinhibition of the SMP domain and facilitates coupling of both tethering and lipid transfer [29]. As the Ca^{2+} -binding C2A domains are also present in E-Syt2 and E-Syt3, their lipid transport ability is likely regulated by the similar mechanism.

Studies of genome-edited HeLa cells that lack all three E-Syts suggested that E-Syts help reverse accumulation of DAG in the PM by transferring it from the PM to the ER for metabolic recycling in response to stimuli that result in the production of DAG in the PM (e.g. hydrolysis of PM $\text{PI}(4,5)\text{P}_2$ by phospholipase C that occurs after the elevation of cytosolic Ca^{2+}) [27]. Nir2 potentially act together with E-Syts to help recycle DAG by exchanging PM phosphatidic acid, a phosphorylated product of DAG, with ER-derived phosphatidylinositol (PI) [31,32]. In pancreatic β cells, PM DAG accumulation stimulates insulin secretion. Ca^{2+} influx resulting from high glucose-induced depolarization of β cells lead to E-Syt1 recruitment to ER-PM contacts followed by reduction of PM DAG. Accordingly, reducing expression of E-Syt1 by RNAi in MIN6 β cells results in increase in PM DAG levels and enhanced insulin secretion [33]. Furthermore, E-Syts triple knock-out HeLa cells exhibit defects in the exposure of PM phosphatidylserine (PS) from the inner to outer leaflet that normally occurs in response to increased levels of cytosolic Ca^{2+} [29]. These results further support the critical role of E-Syts in the maintenance of PM lipid homeostasis.

Yeast mutants lacking tricalbins are hypersensitive to inhibitors of sphingolipid biosynthesis, indicating a potential role of tricalbins in sphingolipid metabolism [12]. Mice triple knock-outs of E-Syts, however, are viable and fertile [34,35]. In *Drosophila melanogaster*, ESYT (a fly homolog of E-Syts) was reported to localize to presynaptic ER to regulate neurotransmission and control synaptic growth [36]. *Arabidopsis thaliana* mutants lacking SYT1 (a plant homolog of E-Syts) show increased PM fragility against mechanical stresses and during freeze-thaw cycles (i.e. defects in freezing tolerance), indicating a potential role of SYT1 in the regulation of the biophysical properties of the PM [37–39]. Interestingly, ionic stress in *Arabidopsis thaliana* causes cytoskeletal rearrangements and $\text{PI}(4,5)\text{P}_2$ accumulation at the PM, which then facilitates binding of SYT1 to the PM and expands SYT1-enriched ER-PM contact sites [20]. Physiological functions of E-Syts need further investigation.

TMEM24

Transmembrane protein 24 (TMEM24) is another SMP domain ER protein that localizes to ER-PM contact sites in metazoan (**Figure 1**). TMEM24, anchored to ER membrane through its N-terminal transmembrane domain, possesses a SMP domain followed by a C2 domain and a polybasic segment that mediates the interaction of TMEM24 to the PM [14]. The electrostatic interaction between the polybasic segment and the acidic lipids in the PM is regulated by the phosphorylation and dephosphorylation of the polybasic segment; Ca^{2+} -dependent phosphorylation of the polybasic segment by PKC induces the dissociation of TMEM24 from the PM while its dephosphorylation by calcineurin/PP2B allows TMEM24 to return to the PM [14] (**Figure 1**).

The crystal structure of the TMEM24 SMP domain demonstrates that its hydrophobic cavity is narrower than the E-Syt2 SMP domain, eliminating the seam that opens to the solvent as in the case of the E-Syt2 SMP domain [14] (**Figure 2b**). Biochemical analysis showed that TMEM24 SMP domain dimerizes and binds one lipid molecule per monomer instead of two lipid molecules per monomer in the case of the E-Syt2 SMP domain [13,14]. Interestingly, mass spectrometry analysis of the lipid species bound to TMEM24 SMP domain isolated from Expi293 cells revealed the significant enrichment of phosphatidylinositol (PI) compared to other lipid species. This was further supported by cell-free lipid transfer assays where TMEM24 transferred PI more efficiently compared to PS and phosphatidylethanolamine (PE)

[14]. In cells, acute recruitment of TMEM24 to ER-PM contacts by optogenetic manipulation results in the increase of PM PI4P and PI(4,5)P₂ (the phosphorylated products of PI [40]), supporting the role of TMEM24 in transporting/shuttling PI from the ER to the PM via its SMP domain [14] (**Figure 1**).

TMEM24 is highly expressed in pancreatic islets [41]. INS-1 (a cell line derived from pancreatic islets) cells lacking TMEM24 show reduced Ca²⁺ oscillations and reduced insulin secretion when cells are stimulated by high glucose, indicating a key role of TMEM24 in the regulation of glucose-stimulated insulin secretion from the pancreatic β -cells [14,41]. As the localization of TMEM24 to ER-PM contacts is regulated by Ca²⁺-dependent phosphorylation/dephosphorylation cycle, the levels of cytosolic Ca²⁺ are likely to control TMEM24-dependent PI transport to the PM. Accordingly, TMEM24 may function to replenish PI4P and PI(4,5)P₂ in the PM during glucose stimulation. TMEM24 is also enriched in neurons, with its expression increasing in parallel with brain maturation [42]. TMEM24 populates at ER-PM contacts in resting neurons. Overexpression of TMEM24 in neurons induces the expansion of ER-PM contacts, supporting its direct role in tethering neuronal ER-PM contacts. Stimulation of neurons that result in the elevation of cytosolic Ca²⁺ leads to the dissociation of TMEM24 from the PM and transient redistribution throughout the entire ER. Moreover, Kv2.1 channels, the major delayed rectifier K⁺ channels in the brain, localize to the regions of the PM that are marked by TMEM24-mediated ER-PM contacts. These results suggest the possibility of the regulatory feedback between neuronal excitability and lipid transport mediated by TMEM24 [42].

In addition to TMEM24, mammals possess a closely related paralog, C2CD2, that shares similar domain organization with TMEM24 [11,12,42]. C2CD2 is enriched in liver, pancreatic islets and testis [42]. C2CD2 localizes to ER-PM contacts similar to TMEM24. Further, TMEM24 and C2CD2 form heterodimers. However, the dissociation of C2CD2 from the PM upon Ca²⁺ elevation is weaker than that of TMEM24, possibly due to the reduced number of PKC phosphorylation sites in the C-terminal polybasic segment. While their expression pattern and their sensitivity to cytosolic Ca²⁺ are different, the possibility that C2CD2 and TMEM24 may act redundantly in animal physiology needs further investigation.

3. SMP domain proteins at ER-mitochondria contacts and their bypass pathways

Yeast ERMES complex

Endoplasmic reticulum (ER)-mitochondria encounter structure (ERMES) consists of three SMP domain proteins (Mmm1, Mdm34 and Mdm12), Mdm10, and accessory proteins, including Gem1 and Tom7 [43–47] (**Figure 1**). ERMES components were identified through a screen for yeast mutants that could not grow well without an artificial synthetic ER-mitochondria tethering protein; disruption of a single ERMES component leads to disassembly of the entire complex [48].

Mmm1 is integral to ER membrane, while Mdm10 is an integral outer mitochondrial membrane protein and Mdm34 and Mdm12 are cytosolic proteins [48] (**Figure 1**). As mitochondria is not connected with the vesicular transport, membrane lipids that are essential for mitochondria must be transported to mitochondria via non-vesicular transport, and ERMES has been proposed to play a major role in this process, in particular for the transport of PS from the ER to mitochondria for its conversion to PE [46,48].

Crystallography and electron microscopy studies revealed that the Mdm12-Mmm1 complex forms hetero-tetramer of approximately 210-Å-long and adopts an elongated curved and tubular structure that consists of centrally located Mmm1 dimer with Mdm12 monomers at each end [15,16] (**Figure 2c**). The tetrameric Mdm12-Mmm1 complex possesses a continuous hydrophobic tunnel that opens to the solvent and harbors two glycerolipids per Mmm1 monomer and one glycerolipid per Mdm12 monomer [15,49] (**Figure 1 and 2c**). Using purified proteins and artificial membranes, it was demonstrated that the tetrameric Mdm12-Mmm1 complex transports glycerophospholipids while Mmm1 alone has very little lipid transfer activity. These results highlight the importance of the tetrameric complex formation for the efficient ERMES-dependent lipid transfer [17]. Lysates obtained from yeast mutants lacking Mdm12 or Mmm1 show reduced PS transport activity from the ER to mitochondria and reduced PE biosynthesis in mitochondria, suggesting the critical role of ERMES in PS transfer from the ER to mitochondria [17,50], although its direct involvement in PS transfer still remains elusive [51]. While Mdm12 and Mmm1 bind promiscuously to all glycerophospholipids *in vitro*, the Mdm12-Mmm1 complex does not bind to PE [15,16]. Such selectivity suggests that ERMES may play a role in the selective transport of glycerophospholipids between the ER and mitochondria (**Figure 1**).

Several models have been proposed for the ERMES-dependent lipid transports at ER-mitochondria contacts, including “shuttle” and “tunnel” models. In the shuttle model, the Mdm12-Mmm1 tetramer exchanges lipids between the ER and mitochondria by shuttling the SMP tetramer. In the tunnel model, the Mdm12-Mmm1 tetramer bridges the ER and mitochondria outer membrane (i.e. both ends of the SMP tetramer touch the ER and mitochondria simultaneously) and transfer lipids between them [15–17]. Further studies are needed to address the detailed mechanisms of ERMES-dependent lipid transfer.

While it is becoming increasingly clear that the ERMES is directly involved in lipid transport/exchange between the ER and mitochondria, the physiological functions of ERMES are broad. ERMES forms one to five discrete focal structures per cell at ER-mitochondria contacts [52]. It has been shown that the components of the ERMES are involved in mitochondrial physiology, including the regulation of mtDNA replication, mitochondrial protein import and mitophagy [52–57].

PDZD8

PDZ domain-containing protein 8 (PDZD8) was recently identified to localize to ER-mitochondria contacts [58]. PDZD8 has a N-terminal transmembrane domain that anchors it to the ER followed by various cytosolic domains, including SMP domain, PDZ domain, a split C2 domain (two segments can potentially assemble into a functional domain), C1 domain, and coil-coiled (CC) segment [59] (**Figure 1**). Depletion of PDZD8 in HeLa cells lead to decrease in the number of ER-mitochondria contacts, suggesting that PDZD8 plays a critical role in ER-mitochondria tethering in metazoan [58]. However, it remains unclear how PDZD8 localizes to ER-mitochondria contacts and how it regulates ER-mitochondria tethering.

The SMP domain of PDZD8 is predicted to be structurally similar to the SMP domains of Mdm12 and E-Syt2 based on bioinformatics analysis and structural modeling [58,60]. Yeast mutants lacking Mmm1 show defects in mitochondrial morphology and its inheritance; expression of a chimeric Mmm1 protein that replaces its own SMP domain with the SMP domain of PDZD8 rescued the phenotype, suggesting the role of PDZD8/Mmm1 in the regulation of mitochondrial function.

In mammalian cells, PDZD8 was reported to be critical for the regulation of intracellular Ca²⁺ dynamics [58]. When Ca²⁺ is released from the ER store through the activation of IP3

receptor, PDZD8-mediated ER-mitochondria contacts promote the rapid import of Ca^{2+} to mitochondria [58]. PDZD8 is expressed at high levels in mouse central nervous system throughout the development. Stimulation of PDZD8-deficient mouse cortical pyramidal neurons resulted in altered Ca^{2+} dynamics in dendrites; mitochondrial Ca^{2+} uptake was reduced and cytosolic Ca^{2+} was elevated while ER Ca^{2+} release remained unaffected. Thus, ER-mitochondria contact sites mediated by PDZD8 are important for shaping Ca^{2+} dynamics in dendrites of neurons. The role of the SMP domain of PDZD8 in lipid transport remains unclear, as the ER-mitochondria tethering alone mediated by a synthetic tether was sufficient to support the rapid import of Ca^{2+} to mitochondria in cells lacking PDZD8 [58]. Further studies are needed to elucidate the role of PDZD8 in intracellular lipid transport.

ERMES “bypass” pathways (vCLAMPs and Vps13)

Following the identification of ERMES as a key tether of the ER and mitochondria with an ability to transport/exchange lipids between these organelles, other organelle contacts and proteins that can support the viability of yeast mutants lacking ERMES have been identified. They include vacuole and mitochondria patches (vCLAMPs) and vacuolar sorting-associated protein 13 (Vps13). Here, we discuss the mechanisms of their contribution to the ERMES “bypass” pathways.

vCLAMPs are membrane contact sites formed between vacuole and mitochondria in yeast; they are in part tethered by Ypt7-Vps39-Tom40 complex [61,62]. Overexpression of Vps39 in ERMES mutants partially rescued their growth defects [61]. In contrast, disruption of ERMES (by deletion of either one of the ERMES components) leads to the expansion of vCLAMPs [63]. Furthermore, disruption of both ERMES and vCLAMP results in significant reduction in PE synthesis in mitochondria and accumulation of PS in whole cell lysates [63]. Conversely, deletion of Vps39 results in the increase in the number of ER-mitochondria contacts (marked by Mdm34), suggesting that the dynamic substitution of vCLAMPs and ER-mitochondria contact sites allows yeast to bypass ERMES and transport PS to mitochondria through vCLAMP [63]. vCLAMP is also mediated by another tethering complex that consists of Vps13, an evolutionarily conserved family of proteins in all eukaryotes, and Mcp1, a mitochondrial protein that recruits Vps13 to mitochondria. vCLAMP mediated by Vps13-Mcp1 complex is spatially and functionally distinct from vCLAMP mediated by the Ypt7-Vps39-Tom40 complex [62]. In addition to vCLAMP, Vps13 localizes to nuclear-vacuole junction (NVJ) and mitochondria-endosome contacts in yeast, suggesting its potential importance for the functions of multiple membrane contact sites [64–67].

Yeast mutants lacking both Vps13 and ERMES are synthetically lethal [64,66]. Furthermore, either gain-of-function mutation in Vps13 or overexpression of Mcp1 suppressed the growth defects and mitochondrial phenotypes of ERMES mutants [64–66,68]. Significantly, the crystal structure of N-terminal region of Vps13 from fungus *Chaetomium thermophilum* revealed that this region forms a large hydrophobic cavity that harbors several lipid molecules simultaneously (**Figure 2d**), and *in vitro* lipid transfer assays with liposomes further demonstrated the ability of this region to transport glycerolipids between bilayers [69]. These findings together with the genetic interaction between Vps13, Mcp1 and ERMES strongly suggest that Vps13 and vCLAMPs provide a major route for the transport of lipids to mitochondria in the absence of ERMES.

Mutations of VPS13A and VPS13C (human homologs of Vps13) lead to neurodegenerative disorders, including chorea acanthocytosis and an early onset form of Parkinson’s disease [70–72]. In mammalian cells, VPS13A and VPS13C localize to a wide variety of membrane contact sites, including ER-mitochondria, ER-late endosome and ER-lipid droplet contacts [69,73]. The lack of the conservation of the entire ERMES complex in animals and the critical

importance of Vps13 in human health raise the possibility that Vps13 may play a major role in the lipid transport between the ER and other organelles, including mitochondria, in all eukaryotes.

4. SMP domain proteins at ER-Golgi contacts

Nvj2 / TEX2

Yeast Nvj2 (TEX2/HT008 in mammals) has a N-terminal transmembrane domain followed by a PH domain and a SMP domain, and primarily localizes to the NVJ [12] (**Figure 1**). Furthermore, quantitative proteomics analysis of yeast proteins identified Nvj2 as a protein enriched in tubular ER [74]. When NVJ formation is disrupted (as in the case of cells lacking Nvj1) or ER function is compromised due to ER stress, Nvj2 moves to ER-Golgi contacts [75]. The localization of Nvj2 to ER-Golgi contacts depend on its PH domain as Nvj2 lacking the PH domain shows diffuse localization in the entire ER and fails to localize to ER-Golgi contacts. ER stress leads to the expansion of ER-Golgi contacts in yeast, which requires Nvj2 [75]. Moreover, overexpression of Nvj2 also results in the expansion of these contacts, indicating the role of Nvj2 in driving ER-Golgi tethering [75].

Ceramides that are synthesized *de novo* in ER membranes are transported by vesicular and non-vesicular transport to the Golgi complex, where they are converted into various complex sphingolipids. In mammals, ceramide transport protein (CERT) plays a major role in ceramide transport from the ER to trans Golgi by facilitating its non-vesicular transport at ER-Golgi contacts [76]. However, CERT homologue is not present in yeast, and vesicular transport accounts for ~80% of ceramide transport from the ER to the Golgi complex [77]. Overexpression of Nvj2 can facilitate the biosynthesis of the complex sphingolipids in the Golgi complex in yeast mutants that are defective in vesicular ceramide transport [75]. Furthermore, yeast cell lysates overexpressing Nvj2 produce twice as much sphingolipids (e.g. inositolphosphorylceramide) *in vitro* compared to wild-type cell lysates in the condition where vesicular ceramide transport is inhibited, indicating the direct involvement of Nvj2 in non-vesicular ceramide transport. Nvj2 carrying mutations in the SMP domain that are predicted to reduce its lipid binding ability failed to transport ceramide to Golgi. These results suggest that the SMP domain of Nvj2 can potentially harbor ceramide directly [75].

TEX2 also localizes to tubular ER in mammals [74], and the expression of TEX2 can partially rescue the phenotype of yeast mutants lacking Nvj2 (resistance to a sterol biosynthesis inhibitor) [75], suggesting potential functional conservation of this protein family in ceramide transport. The role of TEX2 in mammalian cell physiology remains unknown.

5. Open questions

Growing evidence has demonstrated the critical roles of the SMP domain proteins in cell physiology. With the combination of various experimental approaches, including high-resolution imaging and genetic/molecular manipulations, the localization dynamics of SMP domain proteins and how they tether the ER and other organelles and the PM are becoming clear. Furthermore, biochemical and structural studies have contributed significantly to our knowledge of SMP domain-dependent lipid transport/exchange. Despite the impressive amount of the new insights, we still do not fully understand the functions of the SMP domain proteins. One of the major challenges in the field of membrane contact sites is the functional redundancy of multiple lipid transfer proteins. It is also the case for SMP domain proteins as evidenced by ERMES and ERMES bypass pathways. Such redundancy makes it difficult to determine the physiological properties of individual SMP domain proteins. In addition, expression of an artificial tether (without lipid transport ability) can partially rescue the

defects that result from the lack of some of the SMP domain proteins at various membrane contacts. Thus, new approaches will be needed to dissect the physiological functions of this family of proteins in the context of organismal physiology and intracellular lipid transport. Model organisms with reduced gene redundancy, including *C. elegans* and *Drosophila*, may give us further insights into the function of SMP domain proteins in the future.

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Conflict of interests

The authors declare no competing interests.

Figure legends

Figure 1. Evolutionarily conserved SMP domain proteins localize to various membrane contact sites and regulate lipid transport.

ER-PM contacts: E-Syts, anchored to ER-membrane by a hydrophobic hairpin, form homo and hetero-meric complex and tether the ER and the PM via their C2 domain-dependent interaction with PM PI(4,5)P₂ that is additionally regulated by cytosolic Ca²⁺. E-Syts transfer glycerolipids between the two membranes by their SMP domain, and both their tethering and lipid transport properties are regulated by PI(4,5)P₂ and Ca²⁺; TMEM24, anchored to ER-membrane by a transmembrane domain, dimerizes and tethers the ER to the PM via its polybasic segment-dependent interaction with the PM that is regulated by Ca²⁺-dependent phosphorylation by PKC and dephosphorylation by PP2B. SMP domain of TMEM24 preferentially binds phosphatidylinositol (PI) and transports it from the ER to the PM. ER-mitochondria contacts: PDZD8, anchored to ER membrane by a transmembrane domain, tether the ER and mitochondria and regulates Ca²⁺ dynamics in neuronal dendrites. The mechanisms of its tethering (and its lipid transfer, potentially mediated by its SMP domain) is elusive; Yeast ERMES complex consists of SMP domain-containing Mdm34, Mdm12 and Mmm1, and Mdm10 and tethers the ER and mitochondria. Mmm1 is an ER protein and Mdm12 is a cytosolic protein, while Mdm10 and Mdm34 are mitochondrial proteins. The ERMES complex is thought to be important for the phosphatidylserine (PS)-phosphatidylethanolamine (PE) cycle between the two organelles via its SMP domains' ability to shuttle glycerophospholipids between the ER and mitochondria. ER-Golgi contacts: Nvj2/TEX2, anchored to ER-membrane by a transmembrane domain, moves between NVJ and ER-Golgi contacts and transport ceramide from the ER to the Golgi potentially via its SMP domain. Its PH domain is required for the localization of Nvj2 to ER-Golgi contacts.

Figure 2. Structures of the SMP domains and N-terminal region of Vps13

(a) Crystal structure of the E-Syt2 SMP domain. It forms a dimer, with bound hydrophobic molecules in its hydrophobic groove (Triton-X100 used for the purification of the domain and diacylglycerol). Green and cyan indicate the two monomers within the dimer. Lipid molecules and the detergents are shown in red. From Schauder et al., Nature, 2014 [13] (b) Hypothetical structure of the SMP domain dimer of TMEM24. Orange and yellow indicate the two monomers within the dimer. Based on Lees, Messa et al., Science, 2017 [14]. (c) Crystal structure of Mdm12-Mmm1 complex bound with glycerophospholipids. Blue and purple indicate monomers of Mdm12 and monomers of Mmm1 within the tetramer, respectively. Phosphate groups of phospholipids are in red. From Jeong et al., 2017 [15]. (d) Crystal structure of the N-terminal region of Vps13. It contains a larger hydrophobic cavity compared to that of the SMP domain. From Kumar, Leonzino et al., 2018 [69] Scale bars, 30 Å.

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Figure 1

Figure 2