Short Review

Recent Advances on Synaptotagmin-Like Mitochondrial-Lipid Binding Protein Domain Containing Lipid Transfer Proteins

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Abstract

The Synaptotagmin-like mitochondrial-lipid binding protein (SMP) domain is found in a group of ER-resident lipid transfer proteins that are recruited to membrane contact sites (MCSs) by adaptors. Deciphering the molecular basis underlying the recruitment of SMP proteins to specific MCS sheds light not only on their cellular localization but also on their biological functions at these sites. Here we summarize recent advances in SMP domain-containing lipid transfer proteins, focusing on a recent study showing the localization, regulation and cellular function of a specific SMP protein named testis expressed protein 2 (Tex2). TMEM55, a potential PIP phosphatase on late endosome/lysosomal (LE/lys) membranes, was identified as an adaptor that enables the recruitment of Tex2 to ER- LE/lys MCS. In addition, we have summarized several important questions about the regulation and physiological functions of Tex2 that remained unanswered.

Keywords

Tex2, TMEM55B, ER-LE/lys MCSs

Introduction

Membrane contact sites (MCS) are microdomains where two organelles are in close proximity (~10–50 nm) and are involved in various cellular functions, including organelle dynamics and biogenesis, Ca^{2+} dynamics, signal transduction and alleviation of lipotoxicity (Phillips and Voeltz, 2016; Prinz et al., 2020; Wu et al., 2018). One of the most fundamental roles of MCS is to mediate non-vesicular lipid transfer, which is carried out by a group of proteins called lipid transfer proteins (LTPs). LTPs can extract membrane lipids and transfer lipids through the aqueous cytosol from donor membranes to acceptor membranes via a hydrophobic module called the lipid transfer domain (LTD). The SMP domain (synaptotagmin-like mitochondrial-lipid binding protein) is a specific LTD found in all branches of eukaryote evolution (Kopec et al., 2010; Schauder et al., 2014; Toulmay and Prinz, 2012) and is found in several LTPs, including components (Mmm1, Mdm12 and Mdm34) of the ER–mitochondrial encounter structure (ERMES), which is ancestral to all eukaryotes but has been lost in several lineages including animals, plants, and SAR (stramenopiles, alveolates and rhizaria) (Flinner et al., 2013; Kornmann et al., 2009; Wideman et al., 2013), extended synaptotagmins (E-Syt1, 2 and 3 in mammals and Tricalbin1, 2, and 3 in yeast) and TMEM24 at the MCS between the endoplasmic reticulum (ER) and the plasma membrane (PM) (Giordano et al., 2013; Manford et al., 2012), PDZD8 (Elbaz-Alon et al., 2020; Gao et al., 2022; Guillen-Samander et al., 2019; Shirane et al., 2020), Tex2 and its yeast homolog Nvj2 (Du et al., 2023) at the ER-late endosome/lysosomal (LE/lys) MCS (Figures 1 & 2A). In the following sections, we will summarize the cellular localizations and biological functions of these SMP LTPs with an emphasis on Tex2.

The ERMES complex

In yeast, the ERMES complex acts as an important modulator of mitochondrial dynamics and function. It consists of the integral membrane protein Mdm10 in the outer mitochondrial membrane (OMM) and three SMP domain-containing proteins (Mdm12, Mdm34, and Mmm1) at ER-mitochondria

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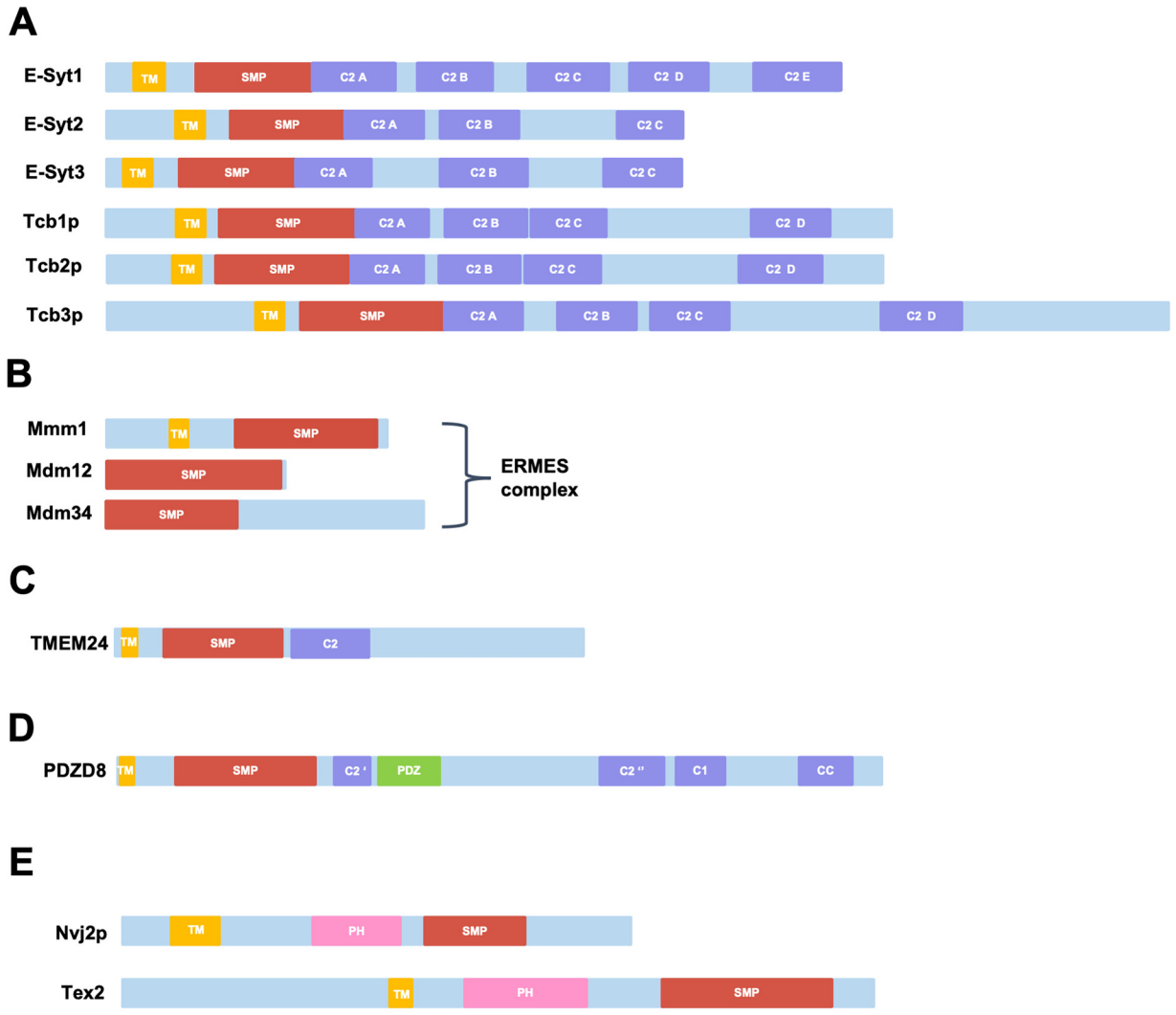

Figure 1. Domain Organization of Lipid Transfer Proteins Containing SMP Domain Including E-Syts/Tcbs (A), ERMES components (B), TMEM24/C2CD2L (C), PDZD8 (D), and Tex2/Nvj2 (E). TM, Transmembrane domain; SMP, Synaptotagmin-like mitochondrial-lipid binding protein; PDZ, Post-synaptic density-95, disks-large and zonula occludens-1; PH, pleckstrin homology; CC, coiled coil.

MCS (Reinisch and De Camilli, 2016). The ERMES complex is essential for mitochondrial morphology and integrity, as loss of the ERMES complex results in spherical mitochondria and loss of their genome during passage (Berger et al., 1997; Burgess et al., 1994; Hobbs et al., 2001; Sogo and Yaffe, 1994). It has been shown that each ER-mitochondria MCS contains approximately 25 discrete bridge-like ERMES complexes distributed irregularly for phospholipid movement between the ER and mitochondria, and each bridge complex contains three SMP domains oriented in a zig-zag arrangement with the SMP domain of Mmm1 adjacent to the ER, Mdm12-SMP in the middle, and Mdm34-SMP close to the OMM (AhYoung et al., 2015; Wozny et al., 2023).

Biochemical analyzes have showed that glycerophospholipids are bound to Mdm12 and Mmm1, particularly phosphatidylcholine (PC) (AhYoung et al., 2015). However, it is still unclear which lipid species ERMES directly transports between the ER and mitochondria. For instance, it remains controversial whether ERMES directly transfers PS from the ER to mitochondria (Kawano et al., 2018; Nguyen et al., 2012).

Importantly, it has been a mystery whether there are homologs of ERMES from yeast in metazoan (Wideman et al., 2013). VPS13A and VPS13D, two members of the bridge-like lipid transfer proteins, have been shown to localize to ER–mitochondria MCS in animal cells (Kumar et al., 2018; Guillen-Samander et al., 2021). Interestingly, both ERMES and VPS13 proteins share a similar bridge-like structure for lipid transfer. However, while VPS13 proteins harbor a single continuous bridge-like tunnel for lipid transport, the bridge-like complex of ERMES is composed of three SMP domains (Mmm1-Mdm12-Mdm34), and the arrangement of the SMP domains could restrain the lipid pathway at the subunit interfaces, unlike in VPS13 proteins,

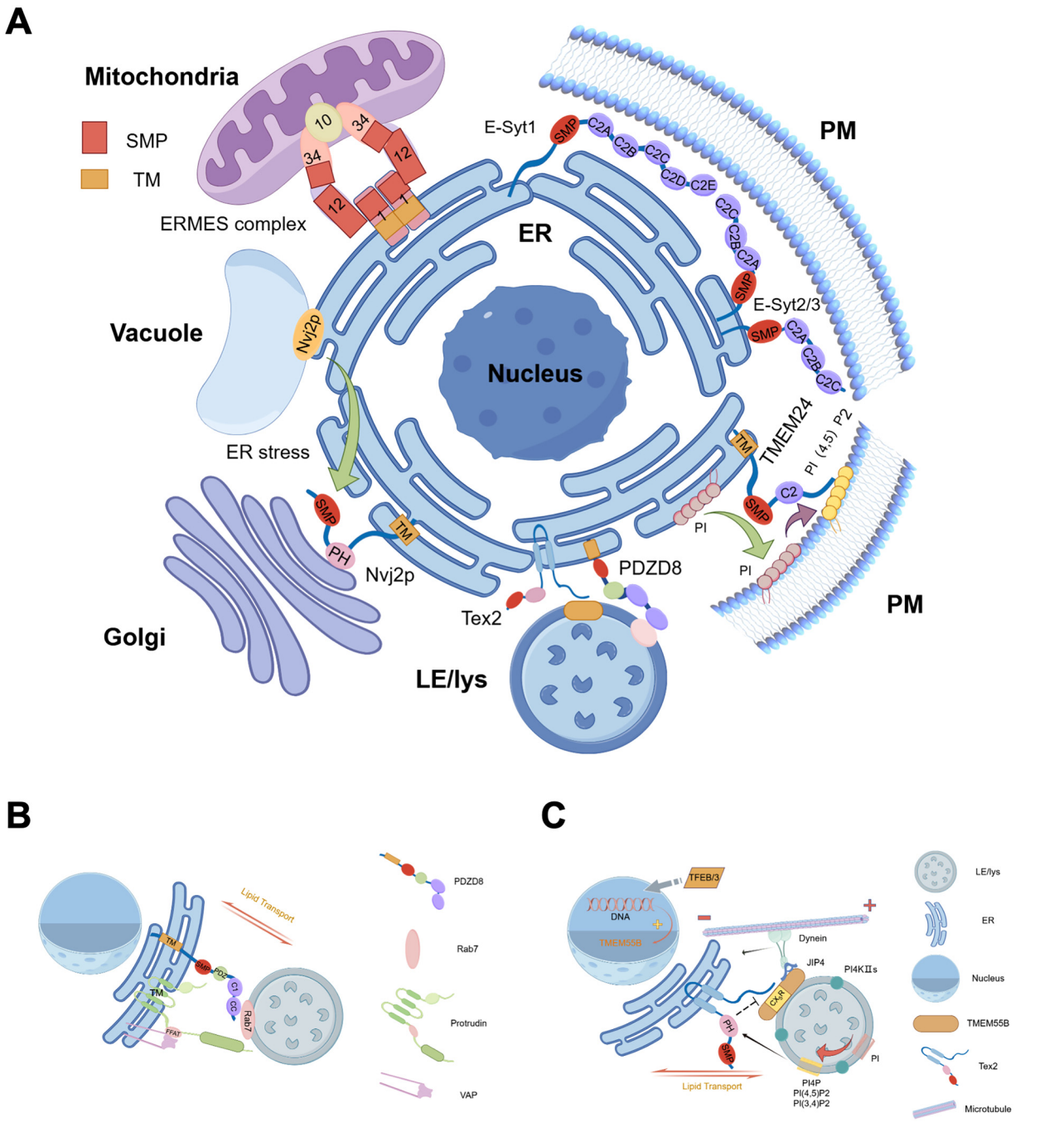

Figure 2. Subcellular localizations of SMP LTPs. (A) Reported localization of SMP proteins in mammalian cells. (B) At ER-LE/lys MCS, PDZD8 is anchored to the ER through the N-terminal TM domain, and recognizes LE/lys via the C1-CC domain by directly binding to Rab7. In addition, PDZD8 interacts with Protrudin at this MCS possibly via the TM domain. (C) The working model of Tex2 at ER-LE/lys MCS. Upon by starvation or cholesterol-induced lysosomal stress, TFEB and TFE3 are activated and translocated to the nucleus to promote the transcription of TMEM55B. TMEM55B binds to JIP4 via a cytoplasmic region independently of the CX_5R motif, promoting dynein-dependent retrograde transport of lysosomes. The Tex2-NT region containing residues 1-277 is necessary for binding to TMEM55B. The PH domain may be involved in the negative regulation of Tex2-TMEM55B interaction via binding to PI4Ps generated by LE-resident PI4KII.

which form large unrestrained conduits (AhYoung et al., 2015; Lees and Reinisch, 2020; Li et al., 2020; Wozny et al., 2023). In addition, unlike ERMES, Vps13 proteins are universal in all eukaryotes with an ERMES-independent but parallel role (John Peter et al., 2017; Lang et al., 2015). Of note, siRNA-mediated depletion of VPS13D, but not VPS13A, resulted in severe defects in mitochondrial morphology (Anding et al., 2018; Du et al., 2021; Wang et al., 2021). In

addition, VPS13D is recruited to ER-mitochondrial MCS by an ERMES regulatory protein Miro (Guillen-Samander et al., 2021), suggesting a potential link of VPS13D to ERMES. Since it is unlikely that a complex homologous to ERMES is present in animal cells, it should be further investigated whether VPS13A, VPS13D or other unknown LTPs play the same roles as ERMES in yeast.

E-Syts/Tricalbins

E-Syts, known as tricalbins in yeast, anchor to the ER membrane by a hydrophobic U-shaped loop in the N-terminal (NT) region, followed by an SMP domain, which is a lipid transfer module and can also mediate E-Syts dimerization together with the hydrophobic loop (Herdman and Moss, 2016). Several C2 domains in the C-terminal region of E-Syts are responsible for targeting to the other membrane. In particular, the C2 domain of E-Syts (the C2C and C2E domains of E-Syt1, the C2C domains of E-Syt2/3) binds to the PM via interactions with $PI(4,5)P_2$ in a Ca^{2+}-dependent manner, which can be achieved by the activation of Ca^{2+} influx from extracellular media, such as Store-Operated Ca^{2+} Entry (SOCE) (Fernández-Busnadiego et al., 2015; Giordano et al., 2013; Idevall-Hagren et al., 2015). Binding of Ca^{2+} to the C2 domains of E-Syts allows for the formation of an arched structure and interaction with the PM, thereby promoting the formation of ER-PM MCS and shortening the distance between the contact sites.

Mass spectrometry analyzes of the lipids bound by the SMP domain of E-Syt2 produced from mammalian cells have shown the presence of glycerolipids, without selectivity for specific head groups (Schauder et al., 2014). E-Syts may cooperate with a phosphatidylinositol-transfer protein Nir2 in the transfer of phosphatidylinositol 4,5-bisphosphate [$PI(4,5)P_2$] and derived metabolites from the PM to the ER in the control of PM lipid homeostasis in response to phospholipase C activation (Kim et al., 2015; Saheki and De Camilli, 2017; Yadav et al., 2015). However, how the E-Syt dimer extracts membrane lipids and the mechanism underlying E-Syt-mediated directional lipid transfer is still unclear.

TMEM24/C2CD2L

Similar to the E-Syts, TMEM24 (also called C2CD2L) is a SMP-containing LTP at ER-PM MCS, and it is mainly expressed in pancreatic β-cells and neurons (Giordano et al., 2013; Lees et al., 2017; Manford et al., 2012; Pottekat et al., 2013; Schauder et al., 2014; Sun et al., 2019). TMEM24 anchors to the ER via its N-terminal TM domain and meanwhile it recognizes the PM by C-terminal unstructured region (Lees et al., 2017), which is regulated by Ca^{2+}, protein kinase C (PKC)-dependent phosphorylation, and diacylglycerol (DAG) (Lees et al., 2017; Sun et al., 2019; Xie et al., 2022). Importantly, TMEM24 preferentially binds phosphatidylinositol (PI) and transfer PI from the ER to the PM, where it can be converted to phosphatidylinositol 4-phosphate (PI4P) and $PI(4,5)P_2$, thereby affecting the coordination of Ca^{2+} oscillations and phosphoinositide signaling pathways that regulate insulin secretion function (Pottekat et al., 2013; Schauder et al., 2014). In addition, TMEM24 affects neuronal differentiation and regulates Ca^{2+} homeostasis as well as mitochondrial ATP production (Sun et al., 2019; Xie et al., 2022).

PDZD8

When it was first described, the SMP protein PDZD8 was thought to be the functional ortholog of Mmm1 of ERMES and that it mediated ER–mitochondria MCS formation in mammalian cells (Hirabayahi et al., 2017). However, it has been proposed that PDZD8 and Mmm1 are more likely paralogs based on phylogenetic analyses (Wideman et al., 2018). Indeed, several studies have showed that PDZD8 interacts and colocalizes with Protrudin (Elbaz-Alon et al., 2020; Gao et al., 2022; Shirane et al., 2020), which is a known ER-LE/lys MCS protein required for lysosomal anterograde transport (Raiborg et al., 2015). PDZD8 anchors the ER via a TM domain in the N-terminal region, and a C1-CC region in the C-terminal binds to Rab7, targeting to LE/lys in a Rab7 activity-dependent manner (Elbaz-Alon et al., 2020; Gao et al., 2022) (Figure 2B). Importantly, the SMP domain of PDZD8 can bind glycerophospholipids and ceramides both in cells and in vitro, and can transfer these lipids in vitro (Gao et al., 2022). The lipid transfer activity of PDZD8 is required for endosome maturation, neurite outgrowth, and neuronal polarity and integrity (Al-Amri et al., 2022; Hewitt et al., 2022; Liu et al., 2023; Thakur and O'Connor-Giles, 2023). In addition, PDZD8 has also been shown to cooperate with another SMP protein Tex2 (see below) and regulates endosomal $PI(4,5)P_2$ homeostasis in *C. elegans* via its SMP domain (Jeyasimman et al., 2021).

Tex2/Nvj2

Nvj2 is an SMP domain-containing protein in yeast consisting of two transmembrane helices followed by a pleckstrin homology (PH) domain and an SMP domain (Toulmay and Prinz, 2012). Nvj2 is distributed over the ER with a moderate enrichment at nucleus-vacuole junctions (NVJs) (Huh et al., 2003; Pan et al., 2000; Toulmay and Prinz, 2012). Importantly, upon ER stress, Nvj2 has been shown to relocate from the NVJs to ER-Golgi MCS in response to an increase in ceramide levels in the ER and mediates ceramide transport from the ER to the Golgi for the synthesis of sphingolipids, preventing the accumulation of this toxic intermediate lipid in the ER (Gallego et al., 2010; Liu et al., 2017). In addition, Nvj2 may directly regulate sphingolipid distribution which in turn play a role in sterol transport or signaling pathways at the NVJs (Gallego et al., 2010; Toulmay and Prinz, 2012).

As a homologous protein of Nvj2 in metazoan, Tex2 shares a similar domain organization as Nvj2. Tex2 contains a disordered region in the NT, followed by two transmembrane helices, a PH domain and an SMP domain in the C-terminal (CT). As mentioned above, Tex2 has been shown to collaborate with PDZD8 and the PI(4,5)P_2 phosphatases OCRL-1 and UNC-26/synaptojanin to regulate endosomal PI(4,5)P_2 homeostasis in worms (Jeyasimman et al., 2021). However, its localization and function are still largely unknown. A recent study has shown that Tex2 is specifically localized to ER tubules (Du et al., 2023). Since ER tubules are the main sites for lipid synthesis in cells, we speculate that Tex2 likely plays a role in the transport of lipids synthesized in the ER.

As a potential LTP on ER tubules, Tex2 is likely recruited to ER-associated MCSs. Using coIP-MS followed by high-throughput imaging screening, TMEM55B is identified as a Tex2-interacting protein that can recruit Tex2 to ER-LE/lys MCS. TMEM55A, the paralog of TMEM55B, can recruit Tex2 to ER-LE/lys MCS as well. TMEM55B is reported to be a weak phosphatase that converts PI (4,5) P_2 to PI5P in LE/lys membranes and cooperates with a motor adapter, JNK-interacting proteins 4 (JIP4), to promote retrograde LE/lys transport (Willett et al., 2017). Dissection of Tex2 and TMEM55B has demonstrated that the recruitment of Tex2 by TMEM55B is mediated by a disordered region in the NT of Tex2 and a highly conserved catalytic motif CX_5R in the phosphatase domain of TMEM55B. Of note, neither the PH domain of Tex2 nor the phosphatase activity of TMEM55B is essential for the recruitment. Interestingly, the kinase activity of PI4KII, which can convert PI into PI4P on LE/lys membranes, significantly inhibits the recruitment of Tex2 by TMEM55B in a Tex2-PH domain-dependent manner, suggesting that the PIPs produced by PI4KII can bind to the PH domain of Tex2 and thereby hinders the Tex2-TMEM55B interaction (Figure 2C).

Tex2 and Nvj2 share a similar domain organization, and both proteins can transfer ceramide (Du et al., 2023), (Liu et al., 2017), supporting the idea that these two proteins are functional orthologs. However, in contrast to the role of Nvj2 during ER stress (Liu et al., 2017), Tex2 is not required for thapsigargin-induced ER stress and is also not substantially shifted from the ER-LE/lys MCS to the ER-Golgi MCS in HeLa cells. The difference may be attributed to different binding partners between Tex2 and Nvj2. Indeed, there are no orthologs of TMEM55A or TMEM55B in yeast, which may explain why Tex2 and Nvj2 act differently under ER stress.

Importantly, lysosomal function and autophagy are substantially impaired in Tex2 KO HeLa cells. Rescuing experiments show that the SMP domain is strictly required for this function. This result suggests a role of lipid transfer in Tex2 function. However, in addition to lipid transport, the SMP domain also mediates protein dimerization, and therefore it remains unclear which functions of the SMP domain are required for lysosomal function.

Conclusions and Future Perspectives

Regarding the Tex2 localization, the interaction of Tex2-TMEM55B and its physiological functions, there are still some questions that need to be answered. First, given that our results clearly showed that both exogenous and endogenous GFP-Tex2 are localized to ER tubules other than ER sheets (Du et al., 2023), how is Tex2 specifically enriched on ER tubules? The localization of Tex2 on ER tubules appears to be independent of the known ER tubule proteins, including RTN4 or REEP5. Dissection of Tex2 has shown that the transmembrane portion alone is not sufficient for ER tubule localization of Tex2. In contrast, an N-terminal region (residues 277–474) adjacent upstream the transmembrane portion is required and sufficient for Tex2 targeting to ER tubules. However, it is not clear how this region contributes to the localization of Tex2 on ER tubules. Interestingly, other ER-associated SMP-LTPs, such as PDZD8 and E-Syts, are not specifically enriched on ER tubules, raising the question of the functional significance of Tex2 localization to the specific ER domain.

Second, it is controversial whether TMEM55 possesses robust PIPs phosphatase activity. Our unpublished results suggest that the activity of TMEM55B is weak. Of note, the CX_5R motif in TMEM55B differs from other known phosphatases in that there is an isoleucine residue after the arginine, rather than a serine or threonine. This change might be the reason for the decrease in phosphatase activity of TMEM55. Interestingly, there is a moderate increase in PI (4,5) P_2 on the LE/lys membrane in Tex2 KO cells, suggesting that Tex2 may regulate the activity of TMEM55B by binding to the catalytic motif of TMEM55. This hypothesis can be tested by an *in vitro* PIP phosphatase assay with purified Tex2 and TMEM55B.

Third, it is still unclear whether or which specific PIP species are involved in the regulation of Tex2-TMEM55B interaction. Tex2-PH binds to PI4P and PI(4,5)P_2 to a similar extent in vitro, suggesting an involvement of PI4P and PI(4,5)P_2 in the regulation of Tex2-TMEM55B interaction. In vitro assays should be performed to investigate whether PI4P or PI(4,5)P_2 can regulate the binding between purified Tex2 and TMEM55B by binding to the PH domain of Tex2.

It is also unclear whether Tex2 is specifically involved in other cellular and physiological processes in addition to lysosomal digestive functions. Tex2 is highly expressed in the testis, and it has been therefore suggested that Tex2 may be implicated in the biogenesis of the acrosome which is a specialized lysosome-related organelle in spermatozoa that contains hydrolytic enzymes for the process of sperm penetration into the oocyte. However, our unpublished results have shown that male mice with Tex2 KO are fertile, suggesting

that Tex2 is not required for acrosome formation. In addition, a recent study has shown that TMEM55B integrates autophagic flux, lysosomal repair and activation of TFE3 to restore cellular homeostasis in response to oxidative stress. The TFEB/TMEM55B/JIP4 pathway promotes retrograde transport of lysosomes to facilitate fusion between lysosomes and autophagosomes. Is Tex2 involved in these cellular processes? If so, is its lipid transfer activity required? These questions should be further investigated.

Lastly, it is unclear whether and what lipid species Tex2 can transport. Do TMEM55 or PIPs regulate the activity and directionality of Tex2-mediated lipid transfer? To answer these questions, in vitro lipid transfer assays should be performed in the future. The study of Tex2 has only just begun, and further efforts need to be made to investigate the physiological functions of Tex2.

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