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SPOTLIGHT

# Building bridges: BLTP2 forms ER–plasma membrane contact sites

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**Bridge-like lipid-transport protein 2 (BLTP2) transfers lipids at membrane contact sites, but its precise localization is unclear. Dziurdzik et al. and Dai et al. identify and characterize a conserved contact site between the endoplasmic reticulum and the plasma membrane mediated by BLTP2.**

All eukaryotic membranes are composed of a mixture of the three major lipid classes—glycerol phospholipids, sterols, and sphingolipids. Each cellular organelle harbors a unique lipid composition. To maintain this composition, cells have evolved a dedicated machinery that transports lipids between organelles and moves them between the two leaflets of a membrane bilayer. Lipid transfer can occur either by vesicular trafficking or by the action of dedicated lipid-transfer proteins (LTPs) at membrane contact sites. Recent studies show that lipid transport by LTPs far exceeds the rates of vesicular transport (1). The first identified family of LTPs usually extracts one lipid at a time and transports it from one organellar membrane to another. Prominent examples of this shuttle-like LTP class are the extended synaptotagmins, steroidogenic acute regulatory protein-related lipid transfer-like proteins, and the oxysterol-binding proteins. Another recently identified class of LTPs comprises the so-called bridge-like LTPs (BLTPs). These proteins form contact sites between two membranes and assemble rod-like structures consisting of the repeating β-groove domain (2).

The first characterized BLTP family members are the VPS13 proteins (3), which were first identified at ER-mitochondrial contact sites, and the Atg2 protein, which bridges the ER with the phagophore membrane during autophagy. In contrast to shuttle like LTPs, the BLTPs form a hydrophobic groove that allows bulk lipid transfer between two organelles. Besides VPS13 and ATG2, this family also contains three poorly characterized members, BLTP1-3. Two studies now characterize both the yeast and the mammalian BLTP2 orthologs and show that they are targeted to a contact site between the ER and the plasma membrane. The study by Dziurdzik et al. (4) characterizes the binding domains of the yeast family members Fmp27 (Hob1) and Hob2. Both proteins are targeted to the ER by an N-terminal segment that likely represents a transmembrane helix and localize to ER–plasma membrane contact sites. To identify potential proteins that target Fmp27 to the plasma membrane, the group analyzed high-throughput chemogenomics data and found the highest reciprocal correlation between an *FMP27* deletion strain and an uncharacterized gene, *YBL086C*. These often-overlooked datasets are a powerful tool for predicting previously unrecognized protein–protein interactions (5). The authors used elegant biochemical tools to prove the interaction between Fmp27/Hob1 and Ybl086C, which they consequently named Hob-interacting protein 1 (*HOI1*). In a parallel study, Dai et al. (6) show that the mammalian protein BLTP2 also localizes to ER–plasma membrane contact sites. While previous studies suggest that BLTP2 localizes to ER-endosomal contact sites (7), the de Camilli group demonstrated that the major contact occurs between the ER and the plasma membrane, with only occasional links to recycling endosomes after they fuse with the plasma membrane. The group employed elegant cell biological assays to show that BLTP2 is targeted to the ER by an N-terminal transmembrane helix. Their further characterization identifies the mammalian Hoi1 homologs FAM102A and FAM102B as plasma membrane adaptors for BLTP2, thereby forming the contact site. They also show an additional requirement for the plasma membrane signaling lipids phosphatidylinositol phosphates and BAR domain–containing proteins. In addition, both groups use AlphaFold (8) modelling to identify a minimal binding motif in the BLTP2 protein that is sufficient to bind its plasma membrane adaptor (Fig. 1). Both studies assign a lipid transport–related function to BLTP2 at the ER–plasma membrane contact site. Dziurdzik et al. deduce a sterol-related phenotype from the analyzed chemogenomics data based on the correlation of the top hits. By utilizing a fluorescent sterol-binding probe, they observe changes in intracellular sterol distribution. However, because BLTP2 is thought to transport phospholipids, the authors conclude that the sterol phenotype may represent a side effect of altered membrane fluidity caused by disrupted phospholipid transport. This aligns with another recent study that shows BLTP2 depletion reduces plasma membrane phosphatidylethanolamine levels, a lipid known to affect membrane properties (9). Dei et al.

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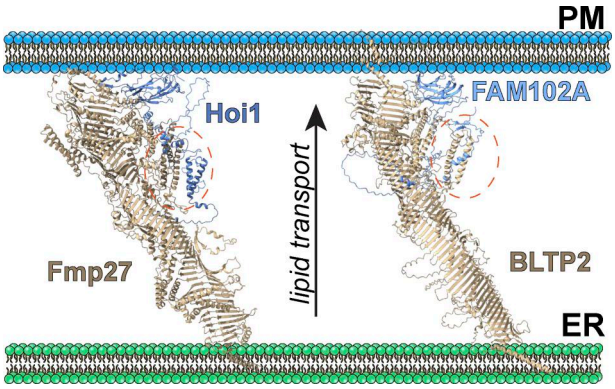


Figure 1. **BLTP2 and its adaptor form a contact site between the ER and the plasma membrane.** AlphaFold 3 (8) predictions of the Fmp27/Hoi1 complex and the BLTP2/FAM102A complex are shown on model bilayers representing the ER (green headgroups) and the plasma membrane (blue headgroups). The adaptor proteins interact with a hairpin motif in the BLTP2 proteins (red circles). The potential lipid transport occurs in the direction of the plasma membrane.

demonstrate that BLTP2 depletion in mammalian cells leads to the accumulation of plasma membrane–attached intracellular vacuoles, a phenotype they attribute to the loss of phospholipid transport. Together, both studies identify a highly conserved membrane contact site between the ER and the plasma membrane, with core components comprising ER-anchored BLTP2 and the plasma membrane adaptors Hoi1/FAM102A/B.

One of the major challenges in studying protein-mediated lipid transport at organelle contact sites remains the *in vivo* measurement of lipid transfer because the community lacks tools to quantify lipid transport. Elegant approaches such as bi- and trifunctional (1) lipids and highly innovative mass spectrometry methods pave the way, yet the kinetics of lipid transport continue to pose a significant obstacle (10). In addition, deciphering the molecular mechanism of BLTPs requires a combination of molecular dynamics simulations and *in vitro* reconstitution assays (11, *Preprint*, 12). Together, these tools will allow to answer key future questions in BLTP biology, namely: (1) what is the lipid specificity of BLTPs, (2) what is the molecular mechanism of lipid uptake and release from BLTPs, and (3) do BLTPs require physical interactions with cofactors such as lipid scramblases. Finally, a further major challenge lies in understanding how the actions of the various LTPs in cells are regulated and coordinated to allow the cell to maintain its organellar lipid code. The two studies by Dziurdzik et al. and Dai et al. represent two further important pieces in solving this molecular puzzle.

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