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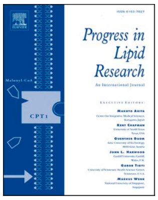

Review Article

# The plant lipid contactome: emerging roles of inter-organelle contact sites in lipid metabolism

Carolina Huercano [a,1], Miriam Moya-Barrientos [a,1], Oliver Cuevas [a], Carlos Cardenas [a], Joaquín J. Salas [b], Victoria Sanchez-Vera [a], Noemi Ruiz-Lopez [a,*]

[a] Instituto de Hortofruticultura Subtropical y Mediterránea "La Mayora", Universidad de Málaga-Consejo Superior de Investigaciones Científicas (IHSM-UMA-CSIC), Universidad de Málaga, Campus de Teatinos, Málaga 29071, Spain
[b] Instituto de la Grasa (IG-CSIC), Edificio 46, Campus Universitario Pablo de Olavide, Ctra. De Utrera Km 1, 41013 Seville, Spain.

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ABSTRACT

Membrane contact sites (MCSs) are fundamental hubs of inter-organelle communication that mediate the non-vesicular exchange of lipids, ions, and metabolites, thereby sustaining cellular homeostasis. In plants, the "contactome"—the dynamic network of all membrane contact sites—has evolved distinctive features to accommodate the requirements of a sessile, photosynthetic lifestyle and the presence of plastids. Within this network, the endoplasmic reticulum (ER) functions as a central hub for lipid biosynthesis and distribution, forming functionally important contacts with multiple organelles. Recent advances in high-resolution imaging, lipidomics, and molecular genetics are beginning to uncover the complexity of these inter-organelle connections and their contribution to lipid homeostasis in plants. This review summarizes current knowledge of the plant contactome, with a focus on lipid transfer proteins and lipid-modifying enzymes that maintain lipid balance during organelle biogenesis, plant development, and stress adaptation. Plant lipid transfer at membrane contact sites can be broadly divided into two mechanistic modes: precision-regulated "shuttles," exemplified by the $Ca^{2+}$-dependent SYT1-mediated diacylglycerol transfer at ER–plasma membrane interfaces, and high-capacity lipid transfer mechanisms, such those mediated by ATG2, that support rapid lipid flux during autophagosome biogenesis. Knowledge of lipid metabolism at plant membrane contact sites is still in its initial stages, and many of the underlying mechanisms remain unexplored. Major challenges include understanding how these sites integrate stress responses, metabolic fluxes, and organelle dynamics. Addressing these questions will be essential to unravel the unique aspects of plant lipid biology and may open opportunities for improving stress resilience and metabolic engineering in crops.

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*Abbreviations:* AAPT1/2, Aminoalcoholphosphotransferases 1/2; ABC, ATP-Binding Cassette; ABCD1, ATP-Binding Cassette Subfamily D Member 1; ACBD5, Acyl-CoA Binding Domain-Containing Protein 5; ACD11, Arabidopsis Accelerated Cell Death 11; ACP, Acyl Carrier Protein; ALA10, Aminophospholipid ATPase 10; ALIS5, ALA-Interacting Subunit 5; AtEH/Pan1, *Arabidopsis thaliana* EH-Domain-Containing/Pan1 Protein; ATG, Autophagy-Related Protein; AZA, Azelaic Acid; BLTP, Bridge-Like Lipid Transfer Protein; BnCLIP1, *Brassica napus* Chloroplast-Localized Lipase 1; C1P, ceramide-1-phosphate; CASP, CCAAT-Displacement Protein Alternatively Spliced Product; CDP, Cytidine Diphosphate; CER2, ECERIFERUM 2; CERT, Ceramide Transfer Protein; CHUP1, Chloroplast Unusual Positioning 1; CoA, Coenzyme A; DAG, Diacylglycerol; DGDG, Digalactosyldiacylglycerol; DGK, Diacylglycerol Kinase; DGS1, Digalactosyldiacylglycerol Suppressor 1; EARLI1, Early Aluminum-Induced 1; EHD1, Eps15 Homology Domain-Containing Protein 1; ER, Endoplasmic Reticulum; ERES, Golgi-associated ER exit site; ERMES, ER–Mitochondria Encounter Structure; ESCRT, Endosomal Sorting Complex Required for Transport; ERGIC, ER–Golgi intermediate compartment; *E*-Syt, Extended Synaptotagmin; FAPP1, Phosphatidylinositol 4-Phosphate Adaptor Protein 1; FAS, Fatty Acid Synthase; FFAT, Two Phenylalanines in an Acidic Tract; FREE1, FYVE-Domain Protein Required for Endosomal Sorting 1; GIPCs, glycosylinositolphosphoceramides; GLTP, glycolipid transfer proteins; GPAT, Glycerol-3-Phosphate Acyltransferase; GPI, glycosylphosphatidylinositol; GRAMD, Glucosyltransferases Rab-Like GTPase Activators and Myotubularins Domain; HOB, Hobbit; hVLCFAs, α-Hydroxylated Very-Long-Chain Fatty Acids; Ice2, Intrinsic Compartment of the ER Membrane Protein 2; IEM, Inner Envelope Membrane.

[*] Corresponding author.

*E-mail addresses:* carolinahuercano@uma.es (C. Huercano), miriambarrientos29@uma.es (M. Moya-Barrientos), olivercuevas@uma.es (O. Cuevas), carlos.cardenas@uma.es (C. Cardenas), jjsalas@ig.csic.es (J.J. Salas), victoriasv@uma.es (V. Sanchez-Vera), noemi.ruiz@uma.es (N. Ruiz-Lopez).

[1] These authors contributed equally to this work.

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## 1. Introduction

Cellular homeostasis and adaptation rely on the coordinated activity of distinct organelles. Rather than functioning as isolated units, organelles are embedded in a highly interconnected network that enables the exchange of signals, metabolites, and lipids. Central to this inter-organelle communication are membrane contact sites (MCSs)—specialized regions where two organelle membranes are maintained in close apposition (typically 10–30 nm) by tethers (proteins or lipids), without undergoing fusion [1–8]. In plants, this connectivity is particularly critical to support photosynthetic function, plastid biogenesis and remodeling, membrane expansion during growth and autophagy, and rapid lipid reallocation during abiotic and biotic stress responses. Endoplasmic reticulum (ER)–based contact sites are the most extensively characterized, reflecting the ER's central role as a hub for cellular coordination [9]. Moreover, compared to yeast and metazoans, plants possess unique organelles—most notably plastids—and a prominent central vacuole, adding structural and functional complexity to the plant contactome. While ER–contact sites have been intensively studied in yeast and animal systems, molecular-level characterization of plant contact sites still lags behind these systems [10,11]. This emerging field has expanded rapidly, with plant-focused publications rising since 2010 (Fig. S1). This growth has been driven in part by methodological advances, including super-resolution and live-cell imaging, cryo-electron microscopy, targeted spatial lipidomics, and improved genetic and biochemical tools adapted for plant systems. Building on these discoveries, Calì et al. [12] recently introduced the concept of the 'organelle contactome', defined as the complete and dynamic network of cellular contact sites that reorganizes in response to metabolic conditions.

Historically, plant lipid research focused on enzymes driving biosynthesis and catabolism. With these enzymatic pathways largely resolved, the field is now shifting toward understanding lipid mobilization within the cell—how lipids are transferred between organelles to reach their functional destinations or undergo further modification. Membrane contact sites have emerged as pivotal hubs for this process, providing structural platforms that support non-vesicular lipid transport and underpin lipid homeostasis in plant cells [12]. Recent evidence underscores the significance of these pathways. A recent publication estimated that 85–95 % of plasma membrane (PM) lipids are recycled to the cell interior via non-vesicular routes, highlighting the central role of contact sites in lipid redistribution [13].

The formation and function of membrane contact sites depend on proteins localized to these regions, which can act as tethers (or scaffold proteins), recruitment factors, regulators, and/or effectors [12,14], with individual proteins often performing several of these activities. Tethers bring two organelles into close proximity [15], and they may act promiscuously across different organelles [12]. A prominent example is the VAMP-associated protein (VAP) family, highly conserved scaffold proteins that recruit tethering partners to the ER and promote the formation of membrane contact sites with other organelles (Fig. 1A, *i*) [16]. In plants, VAP27 proteins act both as structural tethers and recruitment organizers of contact site components. Their cytosolic major sperm protein (MSP) domain interacts with proteins containing FFAT (two phenylalanines in an acidic tract) or FFAT-like motifs, thereby establishing the physical bridge that maintains organelle proximity within nanometric distances [17]. Similarly, C2–containing proteins, such as plant synaptotagmins (Fig. 1A, *ii*) [18], function not only as tethers but also as lipid transfer proteins (LTPs). Conversely, sorter or recruitment proteins control which proteins and lipids occupy contact sites by either attracting residents or excluding others. They can act through direct binding, lipid modifications, or by altering membrane properties [14]. For instance, the plant-specific NET3C protein recruits the actin cytoskeleton to ER–PM contact sites [19,20]. Regulator proteins modulate the extent and activity of contact sites, often via post-translational modifications or signaling; [14,21], for example, Miro2 and related GTPases have been implicated in regulating mitochondrial tethering to the ER and analogous regulators are emerging in plants as modulators of organelle interactions [20,22]. Lastly, effector proteins mediate the exchange of ions, lipids, proteins, or metabolites between organelles [14]. Lipid transfer proteins constitute a major subset of effectors and represent a substantial fraction of the contact site proteome [12,23].

Lipid transfer proteins found at membrane contact sites are structurally and mechanistically diverse, yet they can be categorized based on their mode of lipid transport: shuttle-type and bridge-like and transporters. Shuttle-type transporters typically bind one or two lipid molecules within hydrophobic grooves or pockets, extracting lipids from one membrane and delivering them to another by successive lipid-binding and release events [24]. These include (a) tether-associated shuttles (Fig. 1A, *i*), such as members of the oxysterol-binding protein (OSBP)-related protein (ORP) family, characterized by the OSBP-related domain (ORD; Fig. 2C), which mediates sterol and phospholipid binding [25], (b) membrane-anchored shuttle proteins (Fig. 1A, *ii*), exemplified by the synaptotagmin (SYT) family, which contain a synaptotagmin-like mitochondrial lipid-binding protein (SMP) domain (Fig. 2D) involved in glycerolipid transfer, and C2 domains responsible for membrane binding [26]; and (c) soluble shuttle proteins (Fig. 1A, *iii*), such as Sec14p-like (SFH) proteins (Fig. 2B), which bind and transport phospholipids (e.g., phosphatidic acid, PA) [27,28]. Bridge-like transporters (Fig. 1A, *iv*)

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$IP_2/IP_3$, Inositol Phosphates; KCS6, β-Ketoacyl-CoA Synthase 6; LACS, Acyl-CoA Synthetase; LAMs, Lipid Transfer at Membrane Contact Sites; LC3, Microtubule-Associated Protein 1 Light Chain 3; LCBs, long-chain bases; Ldb16, Lipid Droplet Budding Protein 16; Ldo16, Lipid Droplet Protein 16; Ldo45, Lipid Droplet Protein 45; LE, Late endosome; LPA, Lysophosphatidic Acid; LPAT2, Lysophosphatidic Acid Acyltransferase 2; LPCAT, Lysophosphatidylcholine Acyltransferase; LptD, β-Barrel-Shaped Lipid-A Transporter; MAMs, Mitochondria-Associated Membranes; MAP, Myristoylation and Palmitoylation; MCTP, Multiple C2 domain and transmembrane protein; MELL1, LEA-Related LysM Domain Protein 1; MGDG, Monogalactosyldiacylglycerol; MICOS, Mitochondrial Contact Site and Cristae Organizing System; MIEL1, MYB30-Interacting E3 Ligase 1; MIRO2, Mitochondrial Rho GTPase 2; MLT, Mitochondrial Transmembrane Lipoprotein; MSP, Major Sperm Protein; NPC, Non-Specific Phospholipase C; NVJ, Nuclear–Vacuole Junction; OEM, Outer Envelope Membrane; ORD, OSBP-Related Domain; ORP1L, Oxysterol-Binding Protein-Related Protein 1 Long Isoform; ORP, Oxysterol-Binding Protein–Related Protein; OSBP, Oxysterol-Binding Protein; PA, Phosphatidic Acid; PAH, Phosphatidic Acid Hydrolase; PC, Phosphatidylcholine; PD, Plasmodesmata; PDLP5, Plasmodesmata-located protein 5; PE, Phosphatidylethanolamine; PECT, Phosphoethanolamine Cytidylyltransferase; PEX11e, Peroxin 11e; PG, Phosphatidylglycerol; PH, Pleckstrin Homology; PI, Phosphatidylinositol; $PI(4,5)P_2$, Phosphatidylinositol 4,5-Bisphosphate; PI3K, Phosphatidylinositol 3-Kinase; PI4Ks, Phosphatidylinositol 4-Kinases; PI4P, Phosphatidylinositol 4-Phosphate; PLM, PHLOEM UNLOADING MODULATOR; PIPs, Phosphoinositides; PIS, Phosphatidylinositol Synthase; PITP, Phosphatidylinositol Transfer Protein; Pi, Phosphate; PLC, Phospholipase C; PLD, Phospholipase D; PM, Plasma Membrane; PMPs, Peroxisomal Membrane Proteins; PNPLA5, Patatin-Like Phospholipase Domain-Containing Protein 5; PS, Phosphatidylserine; Pdr16, Phosphatidylinositol Transfer Protein 16; PTPIP51, Tyrosine Phosphatase Interacting Protein 51; PUFA, Polyunsaturated Fatty Acid; SAC, Suppressor of Actin; SAR, Systemic Acquired Resistance; SDP1, Sugar-Dependent 1; SH3P2, Src Homology 3 Domain Protein 2; SMP, Synaptotagmin-Like Mitochondrial-Lipid-Binding; SMS1, Sphingomyelin Synthase 1; SQDG, Sulfoquinovosyldiacylglycerol; START, Steroidogenic Acute Regulatory Protein-Related Lipid Transfer; SYTs, Synaptotagmins; TAG, Triacylglycerol; TEX2, Testis Expressed 2; TGD, Trigalactosyldiacylglycerol; TGL4, Triacylglycerol Lipase 4; TGN, Trans-Golgi Network; TML, Themis-Like; TMEM41B, Transmembrane Protein 41B; TOM, Translocase of the Outer Membrane; TULIP, Tubular Lipid-Binding Protein; ULK1, Unc-51-Like Autophagy Activating Kinase 1; Vac8, Vacuolar Surface Protein 8; vCLIP, Vacuolar–Lipid Droplet Contact Site; VAMP, Vesicle-Associated Membrane Protein; VAP, VAMP-Associated Protein; VLCFAs, Very-Long-Chain Fatty Acids; VMP1, Vacuole Membrane Protein 1; VPS, Vacuolar Protein Sorting; WIPI4, WD Repeat Domain Phosphoinositide Interacting 4; Yeh1/2, Yeast Esterase Homolog 1/2..

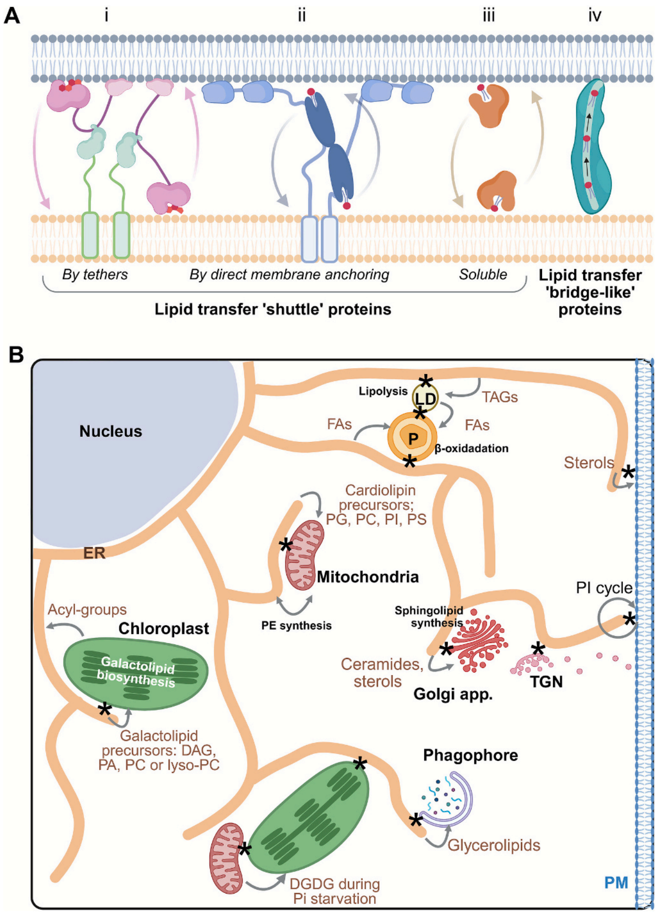

**Fig. 1.** Mechanisms of inter-organelle lipid transfer at membrane contact sites in plants.

(A) Major modes of lipid delivery mediated by lipid transfer proteins. (i–iii) Shuttle-type transporters extract individual lipids from a donor membrane and deliver them to an acceptor membrane via hydrophobic grooves: (i) tether-associated shuttles, (ii) membrane-anchored shuttle proteins, (iii) soluble shuttles. (iv) Bridge-type proteins, form hydrophobic channels enabling high-capacity lipid transfer. (B) Major lipid fluxes at inter-organelle contact sites. The ER serves as a central hub exchanging lipids with multiple organelles. At ER–chloroplast contacts, chloroplasts export acyl groups to the ER for phospholipid synthesis and import galactolipid precursors such as DAG, PA, PC, or lyso-PC. ER–mitochondria contacts support import of PG, PC, PI, PS, and cardiolipin precursors and PE synthesis. Chloroplast–mitochondria contacts enable DGDG transfer during phosphate starvation. Peroxisomes receive fatty acids from the ER or LDs for β-oxidation. LDs store ER-derived TAGs and can release fatty acids back to peroxisomes. ER–phagophore contacts provide lipids for autophagosome expansion. ER–Golgi contacts mediate ceramide and sterol transfer, and ER–plasma membrane contacts regulate phosphoinositide turnover and sterol exchange. Created in BioRender. Ruiz-lopez, N. (2026) https://BioRender.com/s5p3qfq.

Abbreviations: CoA, Coenzyme A; DAG, Diacylglycerol; DGDG, Digalactosyldiacylglycerol; ER, Endoplasmic reticulum; FAs, Fatty acids; Golgi app, Golgi apparatus; LD, Lipid droplet; P, Peroxisome; PA, Phosphatidic acid; PC, Phosphatidylcholine; PE, Phosphatidylethanolamine; PG, Phosphatidylglycerol; Pi, Phosphate; PI, Phosphatidylinositol; PM, Plasma membrane; PS, Phosphatidylserine; SFH5, Sec14-like homolog 5; SYT1, Synaptotagmin 1; TAGs, Triacylglycerols; TGN, Trans-Golgi Network; VAP, Vesicle-associated membrane protein–associated protein.

form elongated, hydrophobic conduits that span the gap between adjacent membranes, enabling high-capacity lipid transfer through direct membrane bridging. Autophagy-related 2 (ATG2) protein (Fig. 2A) serve as a defining example of this class [24,29].

Taken together, the interplay of tethers, regulators and effectors highlights the extraordinary complexity and specificity of the plant 'contactome'. This review aims to synthesize recent insights into the molecular mechanisms of lipid transport at plant membrane contact sites emphasizing both the structural diversity of lipid transfer proteins and their functional roles in organelle biogenesis, stress responses, and plant development. By delineating these plant-specific adaptations within the broader eukaryotic context, we highlight their potential as entry points for improving stress resilience and metabolic engineering in crops.

## 2. ER–PM contact sites: gateways for lipid homeostasis and signal integration

The ER is the central hub of lipid metabolism in eukaryotic cells. It serves as the primary site for the synthesis of most glycerolipids and sterols [30,31], and establishes extensive contacts with virtually every other organelle (Fig. 1B). Through these interactions, the ER is able to distribute lipids throughout the cell via the contactome network. Among the various ER-associated junctions, ER–PM contact sites are perhaps the most intensively studied. They function as critical platforms that integrate extracellular signals with intracellular responses and operate as dynamic hubs where lipid biosynthesis and non-vesicular transport converge [30–33]. Notably, these sites display enhanced capacities for lipid biosynthesis and remodeling compared with bulk ER membranes or isolated PM fraction [34].

The abundance and organization of ER–PM contact sites differ across organisms [3,31,35,36], nevertheless, their conserved role in maintaining lipid homeostasis ensures the proper balance between lipid exchange and compositional distinction of ER and PM membranes. In plants, the microsomal fraction (enriched in ER membranes) is dominated by glycerolipids, which account for more than 80 mol% of total lipids. By contrast, the PM is characterized by a substantial enrichment of phytosterols (~ 30 mol%) and sphingolipids (~ 30 mol%) [37,38]. Although phosphoinositides (PIPs) represent only a minor proportion of PM lipids, they play important roles in regulating key processes such as plant development, reproduction, and immune responses [39–42].

### 2.1. *Coordination of the phosphatidylinositol (PI) cycle and lipid metabolism at ER–PM contact sites*

In plant cells, ER–PM contact sites are key coordination hubs integrating phosphoinositide signaling with lipid biosynthesis. These junctions balance ER lipid output with the dynamic needs of the PM during growth and stress adaptation [31]. A central function of these sites is to sustain the phosphatidylinositol (PI) cycle, which underpins signal transduction.

From a biochemical perspective, phosphatidic acid (PA) is a central intermediate linking phosphoinositide turnover with ER lipid metabolism. Once synthesized in the ER, PA can be channeled into two distinct pathways: it can be converted into cytidine diphosphate diacylglycerol (CDP-DAG) and subsequently used to produce PI (Fig. 3A); or it can be dephosphorylated by lipin/PA hydrolases (PAHs) to yield DAG, which feeds the synthesis of phosphatidylcholine (PC) and phosphatidylethanolamine (PE) [43]. In *Arabidopsis thaliana*, the lipin homologs PAH1 and PAH2 function redundantly at the ER, regulating PA-to-DAG conversion, with loss-of-function mutants displaying altered ER morphology and phospholipid composition [44]. In yeast, PAH1 has been suggested to localize at the ER–PM contact sites, where it contributes to their structural regulation [45,46], underscoring a conserved role of PA metabolism in maintaining membrane contact site function.

In addition to ER synthesis, PA is also generated at the PM under both basal and stress-induced conditions through two main pathways. The first involves phospholipase D (PLD)-mediated hydrolysis (Fig. 3A) of structural phospholipids, such as PC and PE, the major source of PM-derived PA [47]. Plant PLDs exhibit dynamic subcellular localization in response to metabolic, stress and hormonal cues [48–50]. Direct evidence for PLD localization specifically at ER–PM contact sites in plants is lacking, but studies in non-plant systems show that PM-associated PLD activity generates lipid intermediates that are subsequently transported to the ER at ER–PM contact sites [51]. The second pathway is a rapid, stress-response which involves PI-specific phospholipases C (PI-PLCs) to produce DAG [33,52,53]. Fluorescent protein tagging in *A. thaliana* confirms that several PI-PLCs (AtPLC2, AtPLC3, AtPLC5 and AtPLC9) localize at the PM [42], with AtPLC2 acting as the predominant isoform controlling phosphoinositide turnover, during seedling growth and ER stress responses [54]. In animal systems, PLC signaling is spatially coupled to ER–PM contact sites [55–57]. Whether a similar coupling occurs in plants remains as an open question. Notably, plant and animal PI-PLCs have evolved to preferentially utilize different substrates. While animal PI-PLCs primarily hydrolyze PI(4,5)P$_2$, plant PI-PLCs preferentially use PI4P as substrate. Structural and genomic analysis further support that plant PI-PLCs are most similar to the animal PLCζ isoform, lacking the PH domain typical in other animal PI-PLCs [42]. This divergence underscores an evolutionary specialization in PI signaling across kingdoms.

The DAG generated by PI-PLCs is either phosphorylated by DGKs directly at the PM or it is transferred to the ER where it undergoes phosphorylation. The *A. thaliana* DGK family comprises seven members (DGK1–7), grouped into three clusters [58]. Cluster I DGKs (DGK1 and DGK2, Fig. 3A) are ER-anchored and phosphorylate ER-localized DAG at ER–PM contact sites [33,59]. The subcellular localization of other DGKs is less well characterized, as they lack canonical membrane-targeting motifs [52]. Nonetheless, several isoforms show context-dependent localization: DGK5 localizes to the cytosol or nucleus when expressed constitutively [60], but predominantly at the PM under its native promoter [61]. Additionally, DGK4 has been detected in both the cytosol [62] and the ER [63]. Excess DAG can compromise PM integrity by altering membrane curvature and lipid packing, leading to phase separation and loss of lipid asymmetry [33,64]. Additionally, DAG may also be produced at the PM through hydrolysis of other phospholipids by non-specific PLCs (NPCs), like NPC4, especially under stress conditions [65]. To sustain the PI cycle, DAG at the PM must be recycled to PI, PI4P, and PI(4,5)P$_2$ [66]. Because PI is synthesized in the ER—where CDP-DAG synthase and PI synthase are localized [67,68] —but predominantly consumed at the PM [42], efficient intermembrane lipid transfer is essential to maintain lipid homeostasis. In animal cells, proteins such as Nir2 and Extended Synaptotagmins (*E*-Syts) mediate PA and DAG return to the ER, while Nir2/TMEM24 deliver PI back to the PM [66,69,70]. These coordinated fluxes prevent lipid imbalance and ensure continuous PI supply [10,71]. Similar to mammalian E-Syts [71–75], Arabidopsis SYT1 can mediate non-specific glycerolipid transfer in vitro [76], yet it displays a specific in vivo preference for DAG. Consistent with this, *syt1/syt3* double mutants accumulate DAG at the PM [64].

In plants, Synaptotagmins (SYTs, Fig. 3A) are orthologs of mammalian E-Syts and yeast tricalbins, where they function as ER–PM tethers and lipid transfer proteins [77]. Plant SYTs share a conserved modular architecture, comprising an ER-anchored N-terminal transmembrane domain, a SMP domain, and two C-terminal Ca$^{2+}$-binding C2 domains. The presence of the SMP domain places SYTs within the tubular lipid-binding protein (TULIP) superfamily. This domain (Fig. 2D) has been structurally and functionally defined in mammals as a lipid transfer module, containing a central hydrophobic cavity capable of harboring lipids [10,71,72,74,78]. This architecture supports shuttle-type lipid transfer across nanometer-scale membrane gaps that separate apposed membranes at membrane contact sites [79]. In *A. thaliana*, SYTs are classified into two main subfamilies: SYT1-like (SYT1–3) proteins and SYT5-like (SYT4–5) proteins [64,80,81]. In addition, CLB1/SYT7 has been proposed as an atypical SMP-domain containing protein, lacking the second C2 domain but instead containing a coiled-coil region [82]. More recently, SYT6 has been predicted to contain three C2 domains together with a C-terminal coiled-coil region in a preprint article [83], further expanding the architectural diversity of plant SMP-domain proteins. Among all isoforms, SYT1 is by far the best-characterized,

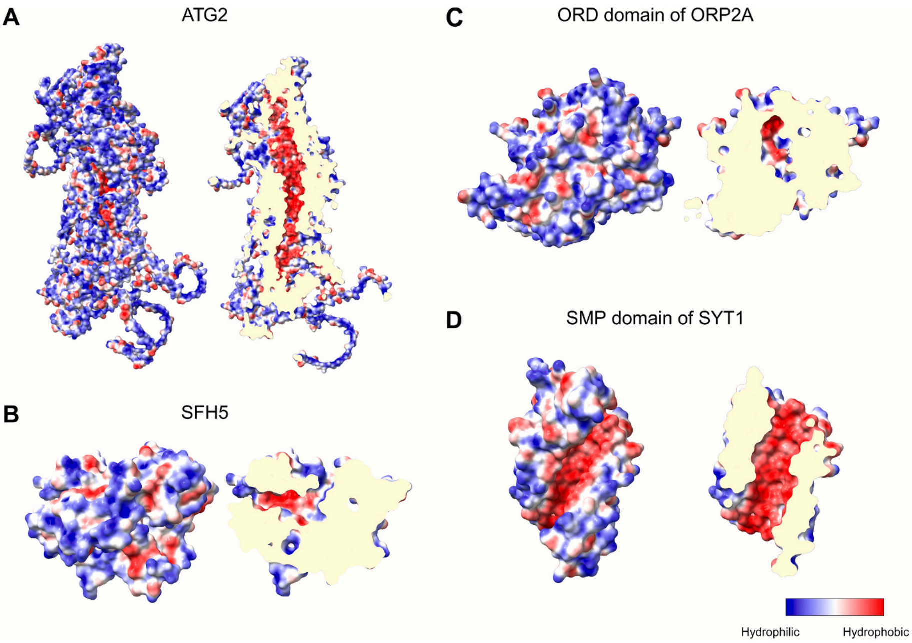

**Fig. 2.** Surface representations of selected lipid transfer proteins, colored by hydrophobicity.
(A) ATG2, (B) SFH5, (C) ORP2 A ORD domain, and (D) SYT1 SMP domain. Panels A, C, and D show AlphaFold structural predictions, whereas panel B is based on the crystal structure (PDB: 7Y11). In each panel, the left panel shows the full protein or domain, and the right panel shows a cross-section highlighting the hydrophobic cavity (in red) that mediates lipid binding and transfer. Hydrophobicity is indicated by the color scale (red, hydrophobic; blue, hydrophilic). These proteins exemplify distinct structural strategies for lipid transfer between membranes. Created in BioRender. Ruiz-lopez, N. (2026) https://BioRender.com/0wgu6ul.
Abbreviations: ATG2, autophagy-related protein 2; SFH5, Sec14-like homolog 5; ORD, oxysterol-binding protein-related domain; ORP2A, oxysterol-binding protein-related 2A; SMP, synaptotagmin-like mitochondrial-lipid–binding protein domain; SYT1, synaptotagmin 1.

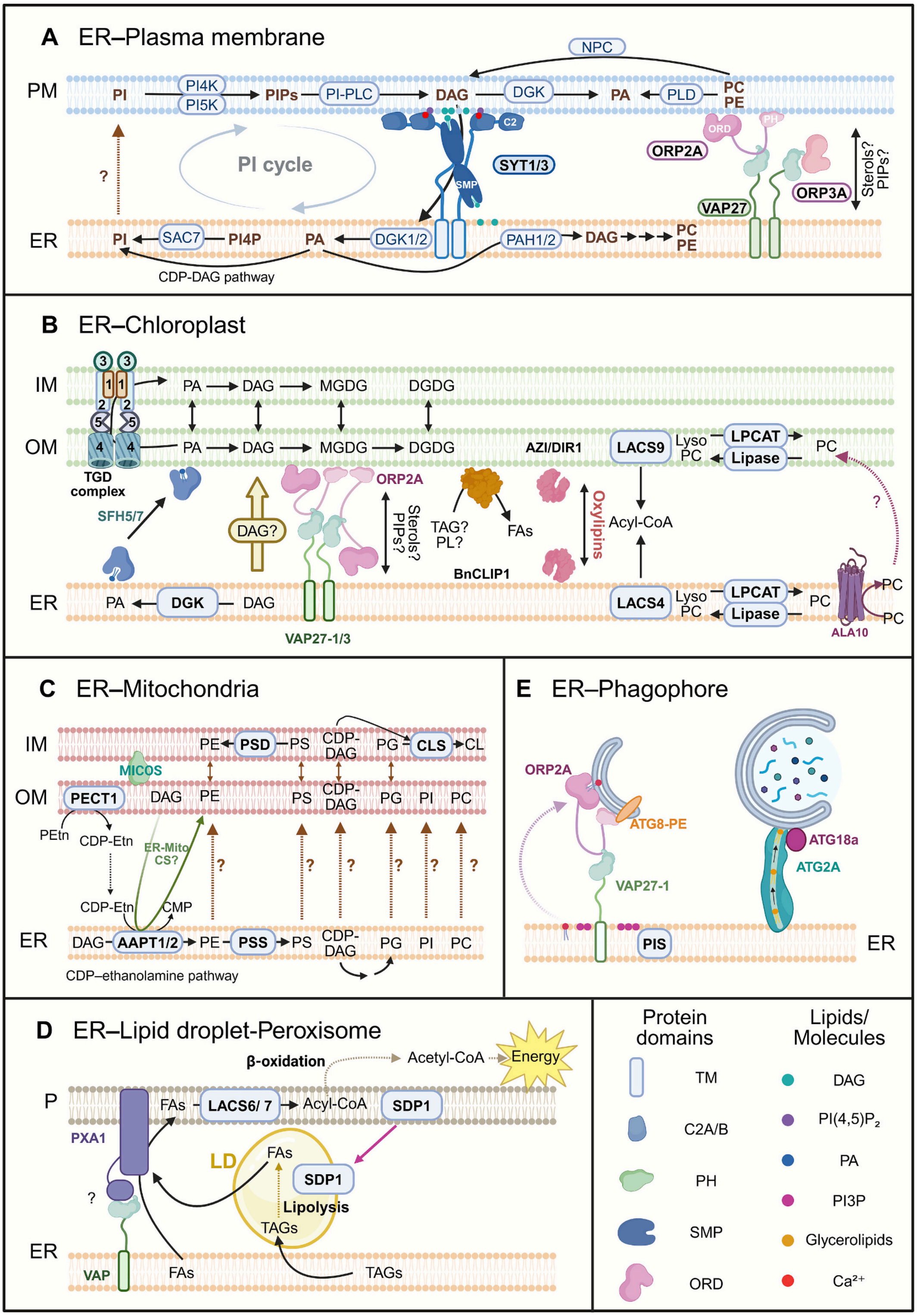

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**Fig. 3.** Lipid metabolism at ER-mediated contact sites in plant cells.
Schematic representation of inter-organelle contact sites showing major lipid fluxes, metabolic enzymes, and lipid transfer proteins. (A) ER–Plasma Membrane (PM): Stress-activated PI-PLC converts PIPs to DAG at the PM, with additional DAG production mediated by NPCs. DAG is transported to the ER via SYT1, which interacts with DGK1/2 to generate PA. PI is regenerated in the ER through the CDP-DAG pathway or SAC proteins (e.g., SAC7) and transported back to the PM by an unidentified lipid transfer protein, where PI kinases restore PIPs. Sterol transport may involve ORP/VAP27 complexes. (B) ER–Chloroplast: PA is delivered from the ER to the chloroplast via the TGD complex and SFH5/7 proteins. DAG, derived from PA, serves as a precursor for galactolipid synthesis. Additional lipid transfer proteins (AZI1, DIR1 and ALA10) and LPCAT-mediated acylation contribute to phospholipid trafficking. Sterol transfer from ER to chloroplast may involve VAP27–ORP2A. (C) ER–Mitochondria: PE synthesis enzymes (PECT and AAPT1/2) are distributed between the ER and mitochondria. Phospholipids such as PS, PG or PE may be transferred from the ER to mitochondria by unidentified lipid transfer proteins, although an *in trans* activity of AAPT enzymes has also been proposed. Cardiolipin is synthesized in the mitochondrial inner membrane from PG and CDP-DAG. (D) ER–Lipid Droplet-peroxisome contacts: TAGs are transferred from the ER to lipid droplets (LDs) for storage. The lipase SDP1, mobilized from peroxisomes, hydrolyzes TAGs within LDs, releasing fatty acids that are subsequently transferred to peroxisomes via the PXA1/VAP complex to fuel β-oxidation. (E) ER–Phagophore: Phagophore nucleation occurs at ER subdomains enriched in PI3P and PIS. The ORP2A/VAP27-1 complex delivers glycerolipids to the expanding autophagosome, interacting with ATG8e. Phagophore expansion is mediated by ATG2. Created in BioRender. Ruiz-lopez, N. (2026) https://BioRender.com/n3s806u
Abbreviations: AAPT1/2, Aminoalcoholphosphotransferases 1/2; ALA10, aminophospholipid ATPase 10; ATG, autophagy-related protein; AZI1, azelaic acid-induced 1; BnCLIP1, *Brassica napus* chloroplast-localized lipase 1; $Ca^{2+}$, calcium ion; CDP, cytidine diphosphate; CL, cardiolipin; CLS, cardiolipin synthetase; CS, contact site; CoA, coenzyme A; DAG, diacylglycerol; DGK, diacylglycerol kinase; DGDG, digalactosyldiacylglycerol; DIR1, defective in induced resistance 1; Etn, ethanolamine; FAs, fatty acids; LACS, long-chain acyl-CoA synthetase; LPCAT, lysophosphatidylcholine acyltransferase; MGDG, monogalactosyldiacylglycerol; MICOS, mitochondrial contact site and cristae organizing system; NPC, non-specific phospholipase C; ORD, oxysterol-binding protein-related domain; ORP, oxysterol-binding protein-related; PA, phosphatidic acid; PAH1/2, phosphatidate phosphatase 1/2; PC, phosphatidylcholine; PE, phosphoethanolamine; PECT, phosphoethanolamine cytidylyltransferase; PH, pleckstrin homology domain; PI, phosphatidylinositol; PI-PLC, phosphoinositide-specific phospholipase C; PI3P, phosphatidylinositol 3-phosphate; PI(4,5)$P_2$, phosphatidylinositol 4,5-bisphosphate; PI4K/PI5K, phosphatidylinositol 4- and 5-kinase; PIP, phosphoinositide; PIS, phosphatidylinositol synthase; PL, phospholipid; PLD, phospholipase D; PM, plasma membrane; PS, phosphatidylserine; PSD, phosphatidylserine decarboxylase; PSS, phosphatidylserine synthase; PXA1, peroxisomal ABC transporter 1; SAC, suppressor of actin; SDP1, sugar-dependent 1 lipase; SFH5/7, Sec14 homolog 5/7; SMP, synaptotagmin-like mitochondrial-lipid-binding protein domain; SYT1, synaptotagmin 1; TAG, triacylglycerol; TGD, trigalactosyldiacylglycerol complex; TM, transmembrane; VAP, vesicle-associated membrane protein-associated protein

with well-established roles in both biotic and abiotic stress responses [81]. Functional redundancy has been reported between SYT1 and SYT3 [64], whereas SYT5 is functionally distinct [80]. AlphaFold-based structural predictions further reveal divergence between the SMP domains of SYT1 and SYT5. The SMP domain of SYT1 exhibits a wider and more open lipid-binding cavity, suggesting differences in lipid cargo selection and transport properties between SYT1- and SYT5-like [80]. Together, these observations highlight a structural and functional diversification of SMP domains within the plant SYT family, underscoring the complexity and regulatory sophistication of lipid transport at ER–PM contact sites in plants.

The lipid transfer activity of SYTs is regulated by $Ca^{2+}$ through their C2 domains [84,85]. Calcium binding alters the electrostatic potential of these domains, increasing affinity for anionic phospholipids and enhancing their PM association. Because SYTs are anchored to the ER via their N-terminal transmembrane domain, their $Ca^{2+}$-dependent interaction with the PM positions them at ER–PM contact sites, where they mediate lipid exchange between the two membranes. In SYT1, this PM interaction involves a canonical $Ca^{2+}$-dependent binding site and is further stabilized by a secondary site recognizing phosphoinositides [85]. Such dual regulation integrates transient $Ca^{2+}$ signals with dynamic phosphoinositide composition at the PM. Under stress, $Ca^{2+}$ elevation drive SYT1 recruitment to the PM, where they mediate DAG transfer to the ER, preventing DAG accumulation and preserving membrane integrity [64]. This mechanism links $Ca^{2+}$ signaling, phosphoinositide status, and lipid metabolism, allowing rapid and localized adaptive responses to environmental stress without perturbing overall membrane composition.

Once in the ER, DAG is phosphorylated by DGK1 and DGK2 to generate PA, re-entering the biosynthetic pathway (Fig. 3A). Recent evidence indicates that SYT1 physically interacts with DGK1 and DGK2, forming a functional complex that channels DAG directly into PA synthesis [33]. This organization creates an efficient metabolic conduit at ER–PM contact sites, minimizing lateral lipid diffusion [33].

However, the phosphatidylinositol transfer protein (PITP) responsible for PI transfer from the ER to the PM in plants remains unidentified. Plants lack direct Nir2/3 or TMEM24 orthologs [83,86], but encode SEC14-like PITPs that may perform analogous functions [87]. Future research should aim to identify and characterize specific SEC14L-PITP isoforms that may operate at ER–PM contact sites to sustain the PI cycle. Once PI is delivered to the PM, it is sequentially phosphorylated by PI-4-kinases, such as PI4Kα1 [88], and PI-5-Kinases, producing PI4P and subsequently PI(4,5)$P_2$ [89].

### *2.2. Dynamic regulation of PI4P gradients by SAC phosphatases at ER–PM contact sites*

Beyond the PI cycle, the ER–PM interface in mammals and yeast hosts a sophisticated counter-transport system driven by a steep PI4P gradient. The PM is enriched in PI4P, while the ER maintains very low levels of this lipid [17]. This gradient is actively maintained by ER-resident Suppressor of Actin (SAC) domain-containing phosphatases, which hydrolyze PI4P returned to the ER [90]. Hydrolysis generates the thermodynamic force required for shuttle transporters, such as OSBPs and ORPs, to move other lipids against their concentration gradients [91]. These proteins extract cargo lipids from the ER, where they are synthesized, and deliver them to target membranes such as the PM. To prevent futile back-transfer, the lipid transfer domain binds PI4P at the target membrane and returns it to the ER, where SAC1 degrades PI4P, ensuring it cannot be recycled [90]. Human SAC1 is predominantly ER-localized but can be recruited to the PM upon activation, contributing to ER–PM contact site formation [91]. This degradation maintains the PI4P gradient that powers the uphill transport of other lipids, preserving the unique composition of the PM.

In plants, the SAC phosphatase family includes phosphoinositide phosphatases that dephosphorylate mono- or bis-phosphorylated phosphoinositides [92–94]. In *A. thaliana* and *Oryza sativa,* nine SAC phosphatases (SAC1–SAC9) have been identified and classified into three subfamilies [95,96]. Subclade II members—AtSAC6, AtSAC7, and AtSAC8—share homology with yeast and mammalian SAC1 and act as functional yeast SAC1 homologs, complementing the cold-sensitive and inositol-auxotrophic phenotypes of *sac1*-null mutants [96–99]. Functionally, AtSAC6–8 regulate PI4P and PI(4,5)$P_2$ homeostasis [100]. Given that PI4P significantly contributes to the negative surface charge of the PM, as demonstrated by MAP-SAC1 assays and pharmacological inhibition [101,102], these SACs may influence membrane electrostatics at ER–PM contact sites. GFP fusion experiments in BY-2 cells indicate that AtSAC6–8 primarily localize to the ER [97]. However, SAC7 (Fig. 3A) exhibits context-dependent subcellular distribution. YFP-SAC7 has been reported at the trans-Golgi network (TGN) in root hairs [94], while another study described SAC7 enrichment at the cortical ER in root meristem and cotyledon epidermal cells, as well as in the apico-basal cortical ER of trichoblasts [103]. In root meristematic cells, SAC7 regulates plasmodesmata and displays the same enrichment at the cortical ER as SYT1 [103]. These observations highlight SAC7's dynamic localization and suggest a specific role in regulating PI4P at ER–PM interfaces.

While direct quantitative evidence for a PI4P-driven counter-transport system at plant ER–PM contact sites is lacking, the system is genetically and biochemically conserved. The plant PM is enriched in PI4P, while the ER contains low levels of this lipid [104], establishing a steep metabolic gradient. Additionally, plant ORPs can bind both PI4P and sterols [16,105–107]. Together, these features provide a molecular framework for PI4P-driven lipid exchange in plants, although its in vivo operation awaits conclusive demonstration.

### 2.3. Emerging bridge-like lipid transfer proteins (BLTPs) at ER–PM contact sites

Bridge-like lipid-transport proteins (BLTPs) are large, conserved eukaryotic proteins, that localize to membrane contact sites, where they are proposed to mediate rapid, bulk transfer of lipids from a donor membrane—often the ER—to a target acceptor membrane [108]. Structural and bioinformatic analysis indicate that BLTPs fold into elongated rod-like molecules, forming a continuous hydrophobic tunnel, generated by repeating β-groove (RBG) domains —the defining feature of the BLTP superfamily. In *A. thaliana*, the best-characterized members of this family are ATG2 (Fig. 2A) and Vacuolar Protein Sorting 13 (VPS13), although neither is present at ER–PM contact sites and will therefore be discussed later in the text.

Nevertheless, in animals, BLTP2 localizes to ER–PM junctions, where it facilitates PE transfer from the ER to the PM, thereby supporting membrane fluidity and lipid homeostasis [17,109]. In *S. cerevisiae,* three BLPT2-related proteins—Hob2, Csf1, and Fmp27—have been predicted as structural orthologs; all localize at ER–PM contact sites, with Fmp27 additionally exhibiting phosphoinositide binding activity [110]. Plant genomes encode several BLTP2-related proteins, including Kinky, Sabre, and APT1 which are required for developmental processes such as root tip formation (*A. thaliana*, *Physcomitrium patens*) and pollen tube growth (*Zea mays*) [111–114]. Their subcellular localization in plants remains unresolved, but insights from yeast and animal models suggest that BLTP2 proteins may provide an alternative route for lipid transfer at ER–PM junctions. In contrast to shuttle-type transporters that mediate selective and tightly regulated lipid exchange, BLTPs are thought to act as conduits for rapid lipid flow. If this mechanism is conserved in plants, it could be particularly important during acute membrane stress or large-scale remodeling, complementing the more finely tuned lipid transport activities of SYTs and ORPs.

### 2.4. Non-vesicular phytosterol transport at the ER–PM interface

Unlike animal PM, where cholesterol is the principal sterol, plant PM contains a complex mixture of phytosterols [115]. In plant cells, sterol biosynthesis occurs in the ER, where only a small fraction of newly synthesized sterols is retained, whereas the PM accumulates up to ~30 mol% sterols [37,115,116]. Sterol delivery to the PM can proceed via vesicular routes—evidence for which derives in part from Brefeldin A sensitivity studies [117] —or by non-vesicular transfer mediated by lipid transfer proteins at membrane contact sites [118].

In yeast and metazoans, non-vesicular sterol transport at ER–PM contact sites involves: (i) Steroidogenic Acute Regulatory protein-related lipid transfer domain-containing proteins (START-like, GRAMD, or LAM-related proteins) and their functional analogs [119–122]; and (ii) ORP proteins (Osh proteins in yeast) [109,123–130]. Plant genomes encode homologs of both groups, yet extensive sequence divergence and functional diversification hinder direct inference of their roles.

Plant START domains have diverged extensively and are frequently fused to homeodomain transcription factors, implying predominant roles in transcriptional regulation rather than direct lipid transfer [131]. Although phylogenetic analyses identify plant proteins related to yeast LAMs and mammalian GRAMD family members [132], none have yet been robustly localized to ER–PM contact sites or shown to mediate sterol flux at these junctions.

By contrast, the plant ORP family presents clearer evidence for contact site roles. *A. thaliana* encodes a dozen ORP paralogs [105,106]. Biochemical studies report that ORP3A binds sitosterol in vitro and associates with VAP27-3 at ER–PM contact sites [17,105]. ORP2A interacts with VAP27-1 shows preferentially binding to phosphoinositides [106,107], phytosterols and monogalactosyldiacylglycerol (MGDG) in vitro [16], and has also been detected at ER–chloroplast [16] and ER–autophagosome [106] contact sites. These observations support a model in which plant ORPs operate via a shuttle-type counter-exchange-mechanism (for example, exchanging phytosterols for PI4P) to sustain PM sterol distribution while preserving PI4P gradients that define membrane identity. The ORD domain (Fig. 2C) within ORP proteins, adopts a conserved β-barrel architecture with a deep hydrophobic cavity that binds a single sterol or phospholipid molecule, allowing ORP proteins to mediate selective lipid extraction and exchange at membrane contact sites [133].

Despite these advances, the molecular mechanisms that underlie non-vesicular sterol trafficking in plants remain incompletely defined. To date, only a subset of ORPs has been biochemically implicated in phytosterol binding or contact site association, and most plant START-domain proteins appear to function in transcriptional control rather than sterol transport. This functional divergence implies that plants may employ alternative sterol carriers yet to be discovered.

### 2.5. Non-vesicular sphingolipid transport at ER–PM contact sites

Sphingolipids are critical determinants of PM identity, signaling, and trafficking, yet their non-vesicular transport in plants remains under-explored relative to glycerolipids and sterols [134,135]. Ceramide-1-phosphate (C1P) transfer proteins, such as *A. thaliana* Accelerated Cell Death 11 (ACD11), have emerged as central regulators of sphingolipid metabolism at membrane contact sites. ACD11 selectively transfers C1P and phyto-C1P between membranes, maintaining sphingolipid homeostasis and modulating processes such as programmed cell death and immune signaling [136,137]. Structurally, ACD11 belongs to the glycolipid transfer proteins (GLTP)-fold superfamily, featuring a phosphate headgroup recognition center and a hydrophobic pocket for acyl chain accommodation, which confers specificity for C1P and phyto-C1P over other sphingolipids [137,138]. Its activity is sensitive to donor membrane composition: phosphatidylserine stimulates transfer, whereas other anionic phospholipids inhibit it, indicating a finely tuned, headgroup-dependent regulatory mechanism at contact sites [139,140]. Functional and biochemical evidence localizes ACD11 predominantly at ER–PM and ER–endosome contact sites, where it interacts with VAP27-1, as well as other membrane-associated proteins such as PRA7 and PRA8 [141]. These interactions, together with its association with membrane fractions, support its recruitment to defined contact sites rather than a cytosolic distribution [141]. Collectively, ACD11 represents a structurally and functionally specialized ceramide/C1P transfer protein that orchestrates sphingolipid metabolism at plant membrane contact sites.

### 2.6. Plasmodesmata as specialized membrane contact sites

Plasmodesmata (PD) are nano-sized, plant-specific intercellular channels that function as membrane contact sites between the ER and PM, bridging adjacent cells and regulating intercellular communication in plants [142–144]. Structurally, PD consist of a tightly tethered ER strand, the desmotubule, within a PM-lined channel, connected by spoke-like elements that maintain ER–PM apposition and cytosolic continuity [142,144,145].

The lipid composition of PD membranes is essential for their function. Lipidomic studies in *A. thaliana* have revealed lateral segregation of lipids along the PD membrane, with enrichment in sterols and sphingolipids containing VLCFAs. These microdomains are crucial for the localization and activity of glycosylphosphatidylinositol (GPI)-anchored proteins and for the regulation of callose deposition, which controls PD permeability [142,144,146]. Detailed analysis of PD sphingolipids has shown enrichment in saturated long-chain bases (LCBs) such as sphinganine (d18:0) and phytosphingosine (t18:0). Functional analysis using double mutants for the sphingoid LCB desaturases SLD1 and SLD2 indicate that t18:0 LCB promotes recruitment of the PD-located protein (PDLP5), triggering callose deposition and PD closure [147–149].

The PHLOEM UNLOADING MODULATOR (PLM), a predicted sphingomyelin synthase, influences PD maturation through regulation of VLCFA-containing ceramides and glycosylinositolphosphoceramides (GIPCs), independently of callose deposition [150]. Additionally, multiple C2 domain and transmembrane proteins (MCTPs 3, 4, and 6) act as ER–PM tethers at PD, with their docking and PD localization controlled by the phosphoinositide PI4P [103]. SAC7, an ER-localized PI4P-phosphatase, modulates MCTP4 accumulation [103], thereby modulating PD-mediated cell-to-cell trafficking in a cell-type-specific manner. Perturbations of sterol composition also impair PD localization of GPI-anchored proteins and alter callose-mediated PD permeability, emphasizing the importance of lipid microdomains in maintaining PD function. Overall, these findings establish PD as multifunctional contact sites whose activity is tightly regulated by lipid metabolism, with sterols and sphingolipids playing central roles in PD function.

### *2.7. Expanding roles of ER–PM contact sites in plant lipid metabolism*

Recent evidence suggests that ER–PM contact sites in plants may coordinate a broader range of lipid metabolic pathways beyond those mentioned above. For example, the ER-resident tether VAP27-1, which is enriched at ER–PM contact sites, physically interacts with the fatty acid elongase KCS6 (β-ketoacyl-CoA synthase 6) and its cofactor CER2 (ECERIFERUM 2), suggesting a spatial link between membrane tethering and very long chain saturated fatty acids (VLCFA) biosynthesis [151]. Although VAP27-1 is a well-established ER–PM tether, the study did not formally demonstrate that these interactions occur within ER–PM membrane contact sites. Consequently, the direct contribution of these membrane contact sites to VLCFA metabolism remain unresolved. Nonetheless, the physical association between VAP27-1 and this key elongation enzymes points to a potential spatial coupling between ER–PM tethering and fatty acid metabolic pathways. This finding also raises the broader possibility that additional lipid-metabolic enzymes may localize to membrane contact sites, where their proximity could facilitate the compartmentalized regulation and coordination of lipid metabolic fluxes.

Collectively, current evidence indicates that while fundamental principles of lipid signaling and transfer at ER–PM contact sites are conserved across eukaryotes, plants exhibit notable divergence from mammalian and yeast systems. This highlights the importance of identifying plant-specific lipid transporters and metabolic modules operating at these contact sites to fully understand their roles in membrane organization, lipid homeostasis, and stress adaptation.

## 3. The ER–chloroplast interface: an assembly line for photosynthetic membranes

Plastids are double-membrane–bounded organelles of endosymbiotic origin that harbor their own genome and perform diverse metabolic functions. Although sharing a common origin, plastids have diversified into specialized types, including chloroplasts, chromoplasts, and leucoplasts [152]. Among these, chloroplasts are the most extensively studied due to their central role in photosynthesis. Chloroplasts comprise three membrane systems: the outer and inner envelope membranes (OEM and IEM), which together form the chloroplast envelope, and the thylakoid membranes. The envelope regulates metabolite, ion, and protein exchange between the cytosol and the stroma, whereas the thylakoids house the protein complexes of the photosynthetic electron transport chain, enabling conversion of light to chemical energy [153,154].

Chloroplast membranes exhibit a highly distinctive lipid composition essential for photosynthetic function. The major lipid classes are the galactolipids monogalactosyldiacylglycerol (MGDG) and digalactosyldiacylglycerol (DGDG), together with the anionic lipids sulfoquinovosyldiacylglycerol (SQDG) and phosphatidylglycerol (PG) [155–157]. Lipid distribution, however, differs between membranes: the OEM is enriched in DGDG and uniquely contains PC, while the IEM and thylakoids are dominated by MGDG, DGDG, SQDG, and PG, displaying a much higher galactolipid-to-phospholipid ratio [157,158]. This specific lipid composition is, in part, maintained by lipid transfer and modifying proteins localized at membrane contact sites, which mediate lipid exchange and remodeling between the ER and chloroplast membranes.

Plant glycerolipid biosynthesis requires coordination between the chloroplast and the ER. In the stroma, fatty acid synthase (FAS) produces acyl–acyl carrier proteins (acyl-ACPs), which can be incorporated directly into plastid lipids through the prokaryotic pathway [157,159]. Alternatively, fatty acids are exported, converted to acyl-CoA in the cytosol, and utilized in the ER to synthesize phospholipids such as PC, in the eukaryotic pathway [43,157,160,161]. Some ER-derived lipids are subsequently re-imported into plastids for galactolipid biosynthesis [160]. The relative contributions of the two pathways vary across species and environmental conditions [157,162].

Because plastids are excluded from the classical vesicular trafficking system, lipid exchange with the ER is thought to rely on non-vesicular mechanisms. Increasing evidence suggests that this transfer is mediated by specialized lipid-binding proteins located at ER–chloroplast membrane contact sites [28,163].

### *3.1. The TGD complex: an inner envelope ABC transporter for phosphatidic acid*

The identification of the first component of the Trigalactosyldiacylglycerol (TGD) complex (Fig. 3B) in plants represented a major advance in understanding lipid transport between the ER and chloroplasts, as well as within chloroplast membranes. The TGD complex was initially characterized through the functional analysis of its core subunits—TGD1, TGD2, and TGD3—which together form an ATP-binding cassette (ABC) transporter localized to the inner envelope membrane of chloroplasts [164]. TGD1, the first subunit identified, is structurally homologous to the permease component of bacterial ABC transporters [165]. The acronym “TGD” reflects the characteristic accumulation of oligogalactolipids in *tgd1* mutants. [166].

Subsequent studies established that TGD1, TGD2, and TGD3 form a stable, high-molecular-mass complex within the IEM [164]. TGD2 possesses a single transmembrane domain that specifically binds PA [167], whereas TGD3 functions as a small ATPase [168]. The TGD complex was later extended with TGD4, an OEM-localized transmembrane lipid-transfer protein [169], and TGD5, a small glycine-rich protein that bridges TGD4 with the TGD1–3 transporter, facilitating lipid transfer across the aqueous intermembrane space [170]. Disruption of any TGD subunit leads to similar phenotypes—deficiencies in ER-derived thylakoid lipids and accumulation of oligogalactolipids and triacylglycerols—highlighting their collective role in lipid trafficking. [170]. Unlike shuttle or bridge mechanisms, the TGD complex functions as an active, processive ABC transporter, driven by ATP hydrolysis via TGD3, effectively acting as a regulated, high-speed “molecular pump.”

Additional complexity in the OEM is suggested by the relationship between TGD4 and LptD1, the two Arabidopsis orthologues of bacterial and plant β-barrel LptD lipid-A transporters. LptD1 protein levels increase under phosphate starvation, and RNAi lines targeting LptD1 display growth defects, particularly in the *tgd4-1* background, which exacerbates sensitivity to light and phosphate stress [171]. In these mutants, the typical induction of DGDG and SQDG under phosphate limitation is reduced. Whether LptD1 functions within the TGD complex or represents a distinct lipid-transfer system at ER–chloroplast contact sites remains unresolved.

Future studies are needed to define the precise molecular interactions among these proteins, potential cooperation with additional partners, and whether they mediate PA transport between the OEM and IEM or from the ER to thylakoids.

### *3.2. BnCLIP1: a lipase at the ER–chloroplast interface*

A key step toward understanding ER–chloroplast lipid trafficking was the identification of *Brassica napus* chloroplast-localized lipase 1 (BnCLIP1 Fig. 3B), a putative lipase inferred from conserved domain phylogeny. Transient expression of BnCLIP1-eGFP in *Nicotiana benthamiana* revealed punctate localization at the chloroplast envelope, particularly enriched at the OEM in close association with the ER [172]. Stable *A. thaliana* lines expressing BnCLIP1-eGFP have since been used as markers of ER–chloroplast contact sites, supporting the notion that transient membrane contacts between the ER and chloroplast envelope underlie their coordinated behavior [173]. Upregulation of BnCLIP1 during seed senescence further suggests a role in chloroplast maintenance and lipid mobilization [172], although its specific lipid targets at the OEM remain unidentified.

### *3.3. The VAP27-ORP2A complex: a tether for sterol and lipid homeostasis*

Compelling evidence for a physical and functional ER–chloroplast association emerged from the identification of a protein complex comprising VAP27-1, VAP27-3, and ORP2A (Fig. 3A) at ER–chloroplast contact sites in *A. thaliana* [16]. This discovery significantly advances our understanding of lipid exchange between these organelles. Live-cell confocal imaging and FRAP revealed that VAP27-1 and VAP27-3 accumulate at ER subdomains adjacent to chloroplasts, exhibiting reduced mobility consistent with stabilization at contact sites. Lipidomic analyses of corresponding mutants showed only minor alterations in overall acyl composition but a marked increase in chloroplast sterols (β-sitosterol and campesterol), indicating that the VAP27-ORP2A complex regulates sterol transport and lipid homeostasis [16].

ORP2A displays a plant-specific adaptation by binding to the plastidial galactolipid MGDG in vitro. Additional studies demonstrated that ORP2A also binds phosphoinositides [106,107] and phytosterols [16], suggesting it may mediate counter-transport of phosphoinositides and sterols while anchoring to chloroplast membranes through MGDG recognition. Acting as a lipid shuttle, ORP2A could selectively transfer sterols and interact with MGDG to maintain chloroplast lipid composition. The specialization of ORP2A for MGDG underscores an evolutionary adaptation of this complex to the unique lipid environment of chloroplast membranes.

### *3.4. Acyl activation and lipid remodeling at ER–chloroplast contact sites: LACS, LPCAT and ALA10*

Several proteins implicated in lipid remodeling have been proposed to operate at ER–chloroplast contact sites. Long-chain acyl-CoA synthetases (LACS) activate fatty acids into acyl-CoAs [174]. In *A. thaliana*, LACS9 (Fig. 3B), localized to the OEM of chloroplast, facilitates plastidial fatty acid export [175,176], whereas LACS4, at the ER membrane [176], functions in parallel [177]. Their subcellular localization suggests both generate acyl-CoA pools at ER–chloroplast contact sites. While single *lacs4* or *lacs9* mutants exhibit no detectable phenotype, the *lacs4 lacs9* double mutant displays impaired ER–chloroplast lipid exchange, reflected by reduced C18:2 enrichment at the *sn*-2 position of MGDG and decreased seed fatty acid content [176].

Lysophosphatidylcholine acyltransferases (LPCATs, Fig. 3B) utilize acyl-CoAs to reacylate lyso-PC into PC, thereby enabling phospholipid acyl remodeling [178]. These enzymes operate bidirectionally and are proposed to remodel PC at ER–chloroplast contact sites, potentially using acyl-CoAs generated by LACS enzymes [179,180]. Interestingly, LPCAT activity was also detected at other contact sites, such as ER–PM junctions [34]. Although initially implicated in MGDG synthesis, recent studies suggest that LPCATs mainly mediate fatty acid incorporation into ER phospholipids and facilitate acyl editing of a chloroplast-derived PC pool destined for export to the ER [176,179,181]. At membrane contact sites, lipid-modifying enzymes and transporters may assemble into “metabolons” that streamline lipid flux. LACS and LPCAT enzymes may thus be physically associated with lipid transfer complexes to form a metabolon that channels fatty acids from chloroplasts directly into ER metabolism.

Finally, the P4-type ATPase flippase ALA10 (Fig. 3B), which is localized to the ER and stabilized by its chaperone ALA-interacting subunit 5 (ALIS5) near chloroplasts, has been suggested to flip C18:2-rich PC from the luminal to the cytosolic leaflet of the ER membrane. This activity may facilitate PC transfer to chloroplasts. Overexpression of ALA10 alters chloroplast PC composition and enhances MGDG biosynthesis at the expense of PC [182], consistent with a role in redirecting lipid flux toward galactolipid synthesis. Further studies are required to fully elucidate the roles of these proteins, confirm their localization at ER–chloroplast contact sites, and determine their precise contributions to lipid transport and remodeling in plant.

### *3.5. Soluble shuttle proteins: facilitating lipid intermembrane transfer*

Several soluble shuttle proteins have been identified at ER–-chloroplast contact sites. SFH5 and SFH7 (Fig. 3B), which contain a conserved Sec14 domain with lipid transfer capacity [183], localize to both ER and chloroplasts via a C-terminal nodulin domain, suggesting a role in ER–chloroplast lipid transport [27]. Crystal structure of the AtSFH5 Sec14 domain (Fig. 2B) revealed one PA molecule within the central cavity in distinct configurations, defining a PA-specific binding mode that contrasts with from the canonical PE/PC/PI recognition of other Sec14 proteins [27]. Double mutants (*sfh5 sfh7*) display defective chloroplast structure, reduced chlorophyll, and decreased chloroplast PA, PC, and PG, impairing MGDG and DGDG synthesis.

In parallel, the lipid transfer proteins AZI1 and EARLI1 are essential for systemic acquired resistance induced by azelaic acid (a C9 oxylipin) [184,185]. These proteins localize to multiple compartments, including the ER, PM, PD [103] and chloroplast OEM. Given that azelaic acid is synthesized in the OEM, it is likely that AZI1 and EARLI1 also operate at ER–chloroplast contact sites [186]. DIR1, identified from systemic acquired resistance-defective *A. thaliana* mutants [187], also localizes at these sites and transports lipid-based defense signals. Collectively, SFH5, SFH7, AZI1, EARLI1, and DIR1 illustrate how lipid transfer at ER–-chloroplast contact sites underpins both chloroplast lipid metabolism and plant immune responses.

### *3.6. Chloroplast–plasma membrane (PM) contact sites*

Strong evidence supports Chloroplast Unusual Positioning 1 (CHUP1) as a key tethering and motility protein at chloroplast–PM contact sites. Together with actin-binding partners, CHUP1 mediates chloroplast positioning to optimize photosynthesis and photoprotection [188–190]. It anchors chloroplast to the PM via an N-terminal outer-envelope insertion domain and a coiled-coil region that stabilizes interactions at cell side walls [188,190]. Although these chloroplast–PM contact sites were first described over two decades ago, to our knowledge no lipid transfer or remodeling proteins have yet been identified at these interfaces, leaving their potential role in intermembrane lipid exchange unresolved.

### 3.7. ER contact sites in non-photosynthetic plastids

While most studies have focused on ER–chloroplast contacts, it is increasingly evident that the ER also engages in interactions with other plastid types, each tailored to the metabolic specialization of the plastid. For amyloplasts, non-photosynthetic leucoplasts involved in starch storage and gravity sensing [191,192], ultrastructural analyses of root cap columella cells revealed a specialized "nodal ER" directly contacting statoliths (specialized amyloplasts), implicating these sites in gravity perception [193,194]. For chromoplasts, which undergo extensive remodeling during fruit ripening to accumulate large quantities of carotenoids [191], direct ultrastructural evidence is limited. The transition from chloroplast to chromoplast, which often entails the complete deconstruction of the photosynthetic thylakoid apparatus and the de novo biogenesis of new carotenoid-sequestering structures [195], is biochemically inconceivable without an exceptionally high degree of cooperation with the ER to synthetize plastoglobules-lipoprotein particle rich in TAGs and carotenoids [196,197]. For etioplasts, which develop in darkness and must assemble a galactolipid-rich prolamellar body as a precursor to the photosynthetic apparatus [198], dependence on the ER is most pronounced. As heterotrophic plastids, etioplasts require lipid precursors imported from the ER via the eukaryotic pathway, making the prolamellar body itself compelling evidence of a highly active ER–etioplast interface.

Although ER contacts extend beyond chloroplasts to diverse plastid types and are likely to mediate specialized lipid exchange, research in this area remains at an early stage. Defining the lipid transporters and remodeling enzymes that operate at these interfaces represents a key challenge and an exciting opportunity for future investigation.

## 4. ER–mitochondria lipid exchange in plants

Mitochondria are dynamic, double-membrane organelles essential for energy production, metabolism, signaling, and programmed cell death [199–201]. Their architecture comprises outer and inner membranes, cristae, and a protein-rich matrix [202]. Mitochondrial membranes exhibit a characteristic lipid composition: PC (~36 mol%) and PE (~37 mol%) are the major constituents, while cardiolipin (CL, ~4 mol %) is uniquely synthesized within mitochondria and concentrated in the inner membrane [203–207], in *A. thaliana* leaves. Plant mitochondria possess a limited capacity for de novo fatty acid synthesis [208,209], and their intrinsic lipid biosynthetic potential is restricted, requiring substantial lipid input from the ER [205,210–212]. Since mitochondria are excluded from vesicular trafficking, lipid exchange is thought to rely on specialized membrane contact sites. ER–mitochondria contact sites have been observed in plants, and although their role in mitochondrial morphology and division is stablished [213,214], their contribution to lipid transfer has not yet been demonstrated.

In mammals, ER–mitochondria contacts (mitochondria-associated membranes, MAMs) host a variety of tethering and lipid-transfer proteins, including VPS13D, Csf1, BLTP1, the ORP5/8–PTPIP51 complex, and Mitoguardin-2 [210,215,216]. In yeast, the best-characterized lipid transfer machinery is the ERMES (ER–Mitochondria Encounter Structure) complex, which comprises four proteins: three SMP-domain proteins (Mmm1, Mdm12, Mdm34) and a β-barrel protein (Mdm10), which together tether the two organelles and mediate phospholipid transfer from the ER to mitochondria [217,218]. Yeast also possesses an alternative tethering structure, the vacuole–mitochondria contact site (vCLAMP), which connects mitochondria to the vacuole. Notably, vCLAMPs are positioned in close proximity to ERMES complexes, and an increase in vCLAMP formation can rescue the growth defects observed in ERMES mutants, indicating functional coordination between these two contact sites [219]. Additional proteins, such as Lam6, act as conserved regulators of yeast ER–mitochondria contacts and are implicated in the regulation of lipid exchange, including sterol transfer, at these sites [220,221].

In plants, mechanistic knowledge is sparse. Identified tethers include MELL1 (Mitochondria–ER-localized LEA-related LysM domain protein 1) in *Physcomitrella patens*, which increases contacts and affects mitochondrial morphology [214,222,223], and the *A. thaliana* proteins Miro2 and TRB1/2, which contribute to contact formation, mitochondrial fusion, and organelle maintenance [22,224]. Notably, neither ERMES nor its metazoan paralog PDZD8 has a plant counterpart [83,215,225], suggesting that plants evolved distinct molecular mechanisms to couple ER and mitochondria, consistent with their unique lipid requirements.

### 4.1. Lipid fluxes at the ER–mitochondria interface

The molecular mechanisms of lipid exchange at ER–mitochondria contact sites in plants remain largely unresolved. Mammalian ORP5 and ORP8 mediate the non-vesicular transfer of PS from the ER to mitochondria, where it is converted into PE by the phosphatidylserine decarboxylase (PSD). ORP5/8 interact with mitochondrial complexes such as MIB/MICOS, which bridge the two mitochondrial membranes, facilitating efficient lipid transfer across the organelle interface [226,227]. Plant ORPs are phylogenetically distinct from mammalian ORP5/8, leaving their role in PS transfer unclear [23,228]. Nevertheless, the underlying metabolic logic appears to be conserved. In plants, the synthesis of key phospholipids—such as PS, PG, PI, and PC—occurs predominantly in the ER [211,229–232] and PE is produced both via the ER-localized CDP–ethanolamine pathway and by mitochondrial PS decarboxylation, with the former predominating (Fig. 3C) [233]. In contrast, in yeast, mitochondrial Psd1 supplies the majority of mitochondrial PE, creating high demand for ER-derived PS [234,235]. Consequently, ER–mitochondria contact sites, such as those formed by the ERMES complex, play a central role in facilitating PS transfer to mitochondria in yeast, whereas in plants, ER-to-mitochondria PS flux appears comparatively reduced. This key metabolic difference provides an explanation for why a dedicated PS transporter analogous to ERMES was not conserved, or never evolved, in the plant kingdom.

Enzyme subcellular localization further suggests tight ER–mitochondria cooperation as the synthesis of PE in plants is split between the ER and mitochondria, requiring the exchange of intermediates. PECT1 (PE-cytidyltransferase 1) localizes to the outer mitochondrial membrane, whereas ER-resident AAPT1/2 (Aminoalcoholphosphotransferases 1/2) catalyze subsequent reactions (Fig. 3C) [236,237]. This spatial distribution raises the possibility that ER enzymes may act *in trans* on DAG at the mitochondrial surface, enabling direct synthesis of PE at contact sites. If this mechanism occurs, direct lipid transfer between mitochondria and other organelles may occur only for specific intermediates, such as DAG or CDP-DAG [205].

While PE flux exemplifies ER–mitochondria cooperation, other mitochondrial lipids, such as PG, also rely on inter-organelle transport to sustain essential mitochondrial functions. PG serves as an essential precursor for cardiolipin biosynthesis and is produced in two steps from CDP–diacylglycerol (CDP–DAG) by the consecutive activities of a PGP synthase (PGPS) and a PGP phosphatase. In *A. thaliana*, PGPS1 localizes to both mitochondria and chloroplasts, while PGPS2 is confined to the ER. The severe chloroplast phenotype of *pgps1* mutants, contrasted with normal mitochondrial structure and lipid composition, suggests that mitochondria could import PG synthesized in the ER [229,238]. However, the lipid transfer proteins mediating this transport have not yet been identified.

Finally, cardiolipin is synthesized in the inner mitochondrial membrane by cardiolipin synthase (CLS), through the condensation of CDP–DAG and PG [239]. The mechanisms by which these precursors are delivered to the inner membrane, and whether intermediates such as PA or DAG participate in this process, remain unclear. In yeast and animals, PA transfer to the inner mitochondrial membrane involves the UPS1/2-Mdm35 complex and the Preli1-Triap1 system, respectively [240,241]. Interestingly, *A. thaliana* encodes orthologs of several proteins involved in intra-mitochondrial lipid trafficking —such as UPS1/2, Tom22, and Tim21—suggesting that these internal pathways are more conserved than those mediating lipid exchange between mitochondria and other organelles. Although cardiolipin synthesis occurs exclusively within mitochondria [203–206,242], some of its precursors, including PG and CDP–DAG, may originate from the ER.

### 4.2. Emerging candidates for lipid transfer at ER–mitochondria contact sites

The absence of ERMES and PDZD8 orthologs in plants underscores an evolutionary divergence at the ER–mitochondria interface, suggesting that plants have evolved alternative mechanisms to sustain non-vesicular lipid exchange between these organelles. Among the most promising candidates are VPS13 proteins, members of the BLTP family, which act as high-capacity lipid transporters through elongated hydrophobic tunnels capable of accommodating multiple glycerolipid molecules simultaneously [243–245].

Phylogenetic and structural analyses have revealed an extensive diversification of VPS13 proteins in *Viridiplantae*. Chlorophytes typically encode three VPS13 paralogs (VPS13M, VPS13S and VPS13Y), whereas Charophytes underwent additional gene duplications, giving rise to as many as six paralogs (VPS13M1, VPS13M2, VPS13S, VPS13Y, VPS13X and VPS13B). In *A. thaliana*, four VPS13 genes are present: AtVPS13M1, AtVPS13M2, AtVPS13S and AtVPS13X. These paralogs differ substantially in domain composition and tunnel architecture. VPS13M proteins possess the longest tunnels (approximately 20–22 nm) and additional non-canonical domains (including PH, C2, β-helix and β-tripod motifs). VPS13S displays a simpler structural organization, whereas VPS13X exhibits a shortened and bent tunnel (~16 nm) and lacks the C-terminal PH domain. Despite this diversification, all VPS13 proteins retain a conserved VAB domain involved in membrane targeting and a continuous hydrophobic tunnel formed by RBG repeats, consistent with a shared role in bulk lipid transport [246,247].

Direct functional evidence supports a role for VPS13 proteins in plant mitochondrial lipid metabolism. A recent preprint [248] reported that *Arabidopsis* VPS13M1 localizes to mitochondria, exhibits broad lipid-binding capabilities, and is required for lipid remodeling during phosphate (Pi) starvation, a condition that triggers extensive membrane reorganization. Loss of VPS13M1 resulted in marked lipidomic changes under Pi limitation, consistent with a role in high-capacity lipid transfer. Interestingly, VPS13M1 shows minimal affinity for plastidial galactolipids. Whether VPS13M1 functions exclusively at ER–mitochondria contact sites or also mediates lipid flux at plastid–mitochondria contacts remains to be determined [248]. Functional specialization among plant VPS13 paralogs is further underscored by genetic studies showing that AtVPS13M2 is required for pollen germination and tube elongation—-processes demanding extensive membrane expansion [249]—while AtVPS13S mutants exhibit sterility and altered root patterning [247]. Together, these data indicate that VPS13 diversification in plants has enabled distinct lipid-transfer functions tailored to developmental and stress-related demands.

Insights from other eukaryotes reinforce this model. In mammalian cells, VPS13D is primarily localized at membrane contact sites where it bridges the ER to mitochondria and peroxisomes. It achieves this by binding to VAP proteins in the ER and interacting with Miro proteins on mitochondria and peroxisomes, facilitating lipid transport between these organelles. Additionally, VPS13D is also enriched at mitochondria–lipid droplet contact sites, where it facilitates fatty acid transfer during metabolic stress. In this context, VPS13D cooperates with the endosomal sorting complex required for transport (ESCRT) component TSG101 to mediate fatty acid flux to mitochondria during starvation, a process that is inhibited by the loss of VPS13D, TSG101, or ESCRT-III [250]. Although ESCRT-dependent lipid transfer has not yet been demonstrated in plants, these parallels emphasize the conserved role of VPS13 proteins as versatile lipid bridges at membrane contact sites.

Recent work has identified the ER stress sensor kinase PERK and one of its lipid-transfer partners (*E*-Syt1), as components of ER-mitochondria contact sites in human cells, opening new perspectives on the molecular mechanisms governing lipid exchange at these interfaces. At these contacts, PERK functions not only as a stress sensor but also as a structural organizer, recruiting E-Syt1 to facilitate phospholipid transfer from the ER to mitochondria. This PERK/E-Syt1 axis sustains the phospholipid flux required for mitochondrial membrane biogenesis and the maintenance of respiratory competence [73]. Although PERK-mediated pathways signaling differs in plants the existence of analogous tethering and lipid-transfer modules may suggest a conserved conceptual framework at ER and mitochondria to enable bulk phospholipid flow.

Together, current evidence suggests that plants may employ a hybrid strategy for lipid transfer at ER-mitochondria contact sites: precursor transfer mediated by VPS13 proteins, possibly complemented by *trans*-acting ER enzymes that remodel lipids directly at contact sites. This model contrasts with the lipid-specific transfer mediated by ERMES in yeast. Although plant-specific tethers such as MELL1 and Miro2 have been identified, the molecular inventory of ER–mitochondria contacts is still incomplete.

### 4.3. Chloroplast–mitochondria contact sites

The existence of physical and functional communication between chloroplasts and mitochondria in plants is widely accepted; however, the molecular architecture of these contacts is not resolved. Highly purified *A. thaliana* mitochondria have reported the presence of plastid-derived lipids and proteins even under stringent isolation conditions [204]. Importantly, as noted by others, such datasets may contain residual plastid contamination, and therefore cannot be taken as definitive biochemical evidence of stable chloroplast–mitochondria membrane contact sites. Nevertheless, these observations have stimulated hypothesis about the existence of persistent physical associations, particularly under environmental conditions that enhance plastid–mitochondria communication.

An example is Pi starvation, a condition in which organellar lipid homeostais is extensively rewired. During Pi starvation, phospholipids levels decline in mitochondria, tonoplast, and PM, whereas plastid-derived DGDG accumulates in these membranes [251–253]. This redistribution requires substantial inter-organelle lipid trafficking. In mitochondria, DGDG transfer is thought to occur at chloroplast–mitochondria contact sites, whose abundance increases approximately threefold in Pi-starved *A. thaliana* cells. Although direct demonstration of lipid transfer at these interfaces is still lacking, mitochondria isolated from Pi-starved cells retain plastid envelope fragments containing MGDG and DGDG synthases, enabling the in vitro synthesis and incorporation of galactoglycerolipids from UDP-[$^{14}$C]galactose [253]. While this may reflect close physical association in vivo, contamination cannot be fully excluded.

Several proteins involved in this process localize within the mitochondrial transmembrane lipoprotein (MTL) complex, which contains outer and inner mitochondrial membrane proteins, as well as plastidial components. DGDG levels in the complex rise during Pi starvation [254]. Additionally, the multi-subunit machinery MICOS (mitochondrial contact site and cristae organizing system) at mitochondria, with Mic60 as a key subunit, links inner and outer mitochondrial membranes and contributes to DGDG import [255]. AtMic60 interacts with outer membrane proteins such as Tom40 to establish intermembrane contact sites. Loss of AtMic60 reduces mitochondrial DGDG import while causing PE accumulation, suggesting a dual role in importing DGDG from plastids and exporting PE for degradation during Pi starvation [254,256,257]. The outer mitochondrial membrane protein DGS1

(DGDG synthase suppressor 1), involved in DGDG metabolism, is also part of this complex, and may participate in connecting mitochondrial architecture to stress-induced lipid remodeling [256]. In addition, two plastid outer envelope proteins, OEP7 and OMP24, are highly enriched in the MTL complex and may contribute to tethering or lipid exchange, though their roles remain to be established [254]. Although still poorly characterized, chloroplast–mitochondria contacts are emerging as central hubs in lipid remodeling, particularly during nutrient stress, with implications for energy balance and organelle homeostasis.

Taken together, the current evidence for chloroplast–mitochondria contact sites in plants remains largely indirect and should be interpreted with caution, particularly in light of the possibility of plastid contamination in mitochondrial preparations. Nonetheless, converging physiological, lipidomic and protein–complex data support a model in which plastid–mitochondria proximity—possibly via yet-undefined tethering factors—facilitates lipid exchange during nutrient stress. These hypotheses remain speculative, but they highlight an emerging concept: chloroplast–mitochondria interfaces may act as dynamic hubs for lipid remodeling, energy balance, and organelle homeostasis, warranting direct mechanistic interrogation in future studies.

## 5. Other ER–centric contacts: Golgi, TGN, late endosomes and vacuole interfaces

The plant endomembrane system comprises several interconnected organelles, including the ER, Golgi apparatus, trans-Golgi network (TGN), early endosomes, late endosomes, lysosome-like compartments, and the central vacuole [258,259]. Together, they form a dynamic network that coordinates protein and lipid trafficking, signaling, and stress responses [9]. Recent advances revealed that these compartments engage in extensive membrane contacts that complement vesicular transport and provide direct routes for metabolite and lipid exchange [9,223]. Below we summarize current knowledge with a focus on interactions supported by solid experimental evidence, while flagging areas that remain speculative and thus require further validation.

### *5.1. Early insights and current perspectives on ER–Golgi contact sites*

Despite the rapid expansion of membrane contact site biology over the past decade, ER–Golgi contacts remain comparatively undercharacterized [260–262]. Plant cell biology provided some of the earliest evidence that the ER and the Golgi apparatus are not only functionally connected through secretion but are also physically and persistently linked. Ultrastructural studies from the 1960s and 1970s revealed that Golgi stacks in plant cells are consistently appressed to the ER. These early observations were later reinforced by live-cell imaging studies, showing that Golgi stacks —although highly motile—maintain a close association with the ER surface and move in coordination with the underlying ER network [263–267]. Together, these foundational studies demonstrated that Golgi stacks likely maintain stable, non-vesicular interactions with the ER.

Recent molecular and imaging studies have begun to translate these ultrastructural observations into mechanistic models. A plant-specific tail-anchored ER protein, MAG3, was identified as a key molecular tether that stabilizes Golgi-associated ER exit sites (ERESs), thereby ensuring efficient cargo and lipid export [268]. In parallel, recent work has demonstrated that ER-to-Golgi transport trafficking in plants proceeds through a dynamic, Golgi-independent *cis*-Golgi tubular network, now recognized as a plant ER–Golgi intermediate compartment (ERGIC). This highly reticulated network forms directly at the ER, remaining physically connected to it, and transiently associates with nascent cis-Golgi cisternae, rather than representing a stable vesicular intermediate. Importantly, its formation and stability are strongly influenced by sphingolipid acyl-chain length, with very-long-chain (C24) ceramides playing a central role in maintaining ER–Golgi connectivity and stabilizing contact interfaces [269]. These findings establish lipid composition as a key structural determinant of ER–Golgi contact site organization and function.

Nevertheless, the molecular composition of ER–Golgi contacts remain largely unresolved across eukaryotes. In mammals, the SMP-domain protein Testis-expressed 2 (TEX2) has been proposed to mediate ceramide transfer at these interfaces, although its physiological relevance is still unclear [18,270]. In yeast, however, the TEX2 homolog Nvj2 functions as a bona fide ER–Golgi tether: it localizes to medial Golgi cisternae and promotes ceramide transfer through its SMP domain, providing compelling evidence for conserved SMP-mediated lipid-exchange mechanisms at these contacts [18,223,270]. In plants, the identity of ER–Golgi tethers remain largely speculative, and only a few candidate tethers have been suggested. One of the earliest candidates, AtCASP—an alternatively spliced isoform of the CCAAT-displacement protein—localizes to cis-Golgi membranes and has been proposed to mediate physical anchoring of Golgi stacks to the ER, potentially facilitating efficient export of nascent secretory cargo [223,271]. Additionally, the Golgi-associated coiled-coil protein Atgolgin-84 A has similarly been suggested as a putative tether, but its mechanistic contribution to ER–Golgi apposition remains unresolved [271,272]. Crucially, no plant-specific lipid transfer proteins have been identified at these contacts, and whether any of the proposed tethers participate directly in lipid exchange is not yet known.

### *5.2. ER–TGN contact sites and lipid homeostasis*

The TGN serves as a central trafficking hub integrating secretory and endocytic routes [273]. Beyond vesicular trafficking, accumulating evidence indicates that ER–TGN contacts are critical for lipid homeostasis. Distinct lipid compositions characterize TGN subdomains: for instance, SYP61-positive secretory vesicles are enriched in hydroxylated very-long-chain fatty acids (hVLCFAs) and sterols, whereas clathrin-coated vesicles exhibit a different lipid profile [258]. Additionally, TGN/early endosomes are enriched in PS, PI4P, and to a lesser extent PI3P [39], suggesting plant-specific regulation of lipid partitioning across TGN subdomains.

Phosphoinositides constitute a central lipid class at the TGN. In plants, PI4P homeostasis is maintained by PI4-kinases and PLC activity, a mechanism distinct from the PI4-kinase/Sac1 system described in mammals [274,275]. Importantly, PLC activity is modulated by sphingolipid acyl-chain length, establishing a feedback loop between sphingolipid metabolism and phosphoinositide signaling that is required for polar cargo sorting, such as auxin efflux carriers [135,274,276]. SAC phosphatases also contribute to TGN lipid regulation: *sac7 sac8* mutants exhibit defects in cargo trafficking, whereas SAC9 localizes to cortical clathrin-coated TGN subdomains, where its loss results in the accumulation of PI(4,5)$P_2$ and consequent impairment of endocytosis [39,100,277].

Sphingolipid trafficking at ER–TGN contact sites remains also poorly understood. Current evidence suggests that vesicular trafficking predominates, with ceramides incorporated into ER-derived vesicles and complex sphingolipids packaged for delivery to their destinations. Perturbation of VLCFA synthesis (e.g., by metazachlor) reduces hVLCFA-based sphingolipids and alters TGN-associated secretory vesicles, linking sphingolipid biosynthesis with TGN trafficking [135,274].

In mammals and yeast, ER–TGN lipid homeostasis is regulated by a diverse array of lipid transfer proteins and lipid-modifying enzymes, including OSBP1, Nir2, ORP9, ORP10, Sec14, ceramide transfer protein (CERT), Kes1/Osh4, and sphingomyelin synthase (SMS1) [25,87,223,260,262,275,278–281]. In plants, evidence remains more limited. Although ORP homologs are present, their activity at ER–TGN contact sites has not been demonstrated yet, likely due to the highly dynamic and sometimes independent nature of the plant TGN [39,274]. The conservation of VAPs and FFAT motifs in plant proteins suggests the potential for CERT-like mechanisms. Indeed, plant ceramide/C1P transfer proteins such as ACD11 have been structurally and biochemically characterized, providing the first evidence for plant-specific ceramide transfer at ER–PM contact sites [137], although a plant CERT mediating ceramide transfer at ER–TGN contact sties has not yet been identified. A recent preprint reported that the SMP-domain protein SYT6 localizes to ER–TGN contact sites, providing the first molecular example of a plant-specific tether at this interface [83] and offering a promising starting point for proteomic and interactome-based discovery strategies.

While the plant TGN shares some functional parallels with its mammalian and yeast counterparts, its lipid composition and regulatory mechanisms reveal plant-specific adaptations and underscore the need for future studies to elucidate how lipid homeostasis is maintained in the plant secretory pathway.

### *5.3. ER–late endosome and ER–vacuole contact sites*

ER–late endosome (LE) and ER–vacuoles contacts represent crucial hubs for lipid exchange and regulation in eukaryotic cells. In yeast and mammalian systems, ER–LE contacts are well-established lipid-exchange interfaces mediated by ORPs, OSBP, NPC1 and other lipid metabolism factors [282–287], as well as by tethering proteins such as Protrudin which integrates Rab and phosphoinositide signals to stabilize these contacts [283,288]. In plants, the molecular characterization of ER–LE contacts is still emerging, yet several lines of evidence support potential lipid-regulatory roles. FYVE-domain proteins (e.g., FYVE-domain protein required for endosomal sorting 1, FREE1) participate in endosomal sorting and membrane remodeling [259,289,290]. Arabidopsis SYT1 partially colocalizes with endosomes hinting at dual targeting [64,291], and VAP27 proteins associate with endosomal membranes and bind clathrin and endocytic lipids, consistent with tethering roles [26,258]. While these observations are suggestive, definitive demonstrations of lipid transfer at plant ER–LE contacts are still needed.

ER–vacuole contacts in plants are even less defined, with little information available on their molecular architecture [26]. Insights from yeast nucleus–vacuole junctions (NVJs) include the perinuclear ER protein Nvj1 and the armadillo repeat vacuolar protein Vac8. These junctions recruit additional proteins, such as Osh1 (ORP protein) which binds the ER through interactions with VAPs (Scs2/Scs22) and the vacuole via its PH domain. Other recruited proteins include the SMP-containing Nvj2 and the lipid enzyme Tsc13 [292,293]. *A. thaliana* lacks an Nvj1 homolog; however, it encodes over one hundred armadillo repeat proteins, raising the possibility of analogous tethering complexes at ER–vacuole contact sites [294].

## 6. The peroxisomal interface

Peroxisomes are dynamic, single-membrane organelles present in most eukaryotes [295]; in plants, they play central roles in primary and secondary metabolism, stress responses, photorespiration, hormone biosynthesis, and lipid catabolism [296,297]. Their dynamic behavior—including elongation, fission, and degradation—depends on continuous communication with other organelles [294]. A conserved peroxisomal function is fatty acid β-oxidation, which in plants and yeasts occurs exclusively within these organelles. In oilseed plants such as *A. thaliana,* β-oxidation relies on the mobilization of TAGs stored in lipid droplets (LDs), underscoring the importance of peroxisome contact sites in coordinating lipid storage, transfer, and utilization [298].

A fundamental interface connects peroxisomes to the ER, which supplies lipids and proteins required for peroxisomal membrane expansion and biogenesis. Electron microscopy studies have long documented the close spatial association between these organelles [299,300], and accumulating evidence indicates that lipid exchange can occur through direct ER–peroxisome contacts rather than exclusively via vesicular trafficking [301]. Although plant-specific mechanisms remain to be elucidated, genetic and imaging studies support the functional relevance of these contacts [302–304]. In mammals, ER–peroxisome tethering is mediated by interaction of the peroxisomal protein ACBD5 with ER-resident VAPB via a FFAT motif, enabling VLCFA transfer to support membrane growth and β-oxidation. In plants, the peroxisomal ABC transporter PXA1 (also known as COMATOSE/PED3) (Fig. 3D) contains a putative FFAT-like motif and has been proposed to engage in analogous interactions with VAP proteins [302], although direct biochemical evidence is still lacking. In addition, mammalian *E*-Syts tether ER membranes to peroxisomes and promote cholesterol transfer [305]. While ER–peroxisome contacts involving plant SYTs have not been demonstrated, their established lipid transfer activity at ER–PM contact sites [64] suggests that related mechanisms may operate at ER–peroxisome interfaces. In yeasts, members of the Pex23 family (PEX24, PEX30, PEX32) tether ER and peroxisomes and facilitate lipid transfer required for peroxisomal membrane expansion [306], but homologs of these proteins are absent from plant genomes [307]. In *Hansenula polymorpha,* loss of Pex23 proteins can be compensated by the large lipid transporter Vps13, which mediates rapid ER-to-peroxisome lipid transfer during biogenesis [308]. Similarly, mammalian VPS13D operates at ER–peroxisome–mitochondria interfaces in cooperation with VAPs and small GTPases [309]. The absence of PEX23 homologs in plants highlights the potential involvement of plant VPS13 orthologs, together with PXA1 and VAP proteins, in mediating ER–peroxisome lipid transfer.

Peroxisomes also establish extensive and dynamic contacts with LDs, particularly during seed germination when TAG reserves must be rapidly mobilized. A notable conceptual advance was the identification of the "ER-nest," a tripartite ER–LD–peroxisome contact site that forms during seed germination [310]. In this structure, ER membranes envelop LDs and tether them to peroxisomes, spatially channeling fatty acids released from TAG hydrolysis directly toward peroxisomal β-oxidation. Such spatial coupling is thought to optimize lipid flux under conditions of high metabolic demand and provides a structural framework for coordinated lipid mobilization [311]. The TAG lipases SUGAR-DEPENDENT1 (SDP1) and SDP1-LIKE play central roles in TAG hydrolysis [312,313], while access of lipases to the LD core is tightly regulated by oleosins, which stabilize the LD surface and restrict enzymatic entry [314,315]. Fatty acids released upon TAG breakdown are subsequently transferred to peroxisomes for β-oxidation, likely via LD–peroxisome contact sites. Microscopy and genetic studies support the existence of these interfaces [316–318], which are particularly prominent during post-germinative growth when TAG degradation fuels energy production and membrane biogenesis [319,320]. During this developmental window, glyoxysomes—specialized peroxisomes of germinating seeds—maintain tight physical associations with LDs, consistent with a model of directed fatty acid transfer. Accordingly, mutants defective in peroxisomal β-oxidation (*ped1*) or TAG lipolysis (*sdp1*) exhibit enlarged peroxisomes with pronounced invaginations at LD interfaces [317,321].

Fatty acid import into peroxisomes is mediated by the ABC transporter PXA1 [313], functionally linking LD-derived fatty acid release to peroxisomal β-oxidation [302,321]. Once imported, fatty acids are activated by LACS6 and LACS7 [322]. The detection of VAP proteins in LD proteomes [323] further supports a model in which conserved VAP–FFAT interactions coordinate fatty acid transfer across ER–LD–peroxisome interfaces, analogous to mechanisms described in other eukaryotes [324].

Finally, peroxisomes frequently associate with chloroplasts, particularly in photosynthetically active tissues where these contacts facilitate photorespiratory metabolism. Nanoscale three-dimensional imaging reveals increased contact surface areas between chloroplasts and peroxisomes, as well as enlarged interfaces among chloroplasts, peroxisomes, and mitochondria under light conditions [325,326]. Functional evidence from *pex*10 mutants supports the physiological relevance of plastid–peroxisome interactions in photorespiration [327], yet their potential contribution in lipid exchange remains largely unexplored. This knowledge gap is particularly relevant during developmental transitions such as seed germination, when peroxisomes function as glyoxysomes and plastids exist as non-photosynthetic etioplasts [191,319], raising the possibility that transient, developmentally regulated contact sites facilitate lipid precursors exchange to support plastid biogenesis.

## 7. The contactome in autophagy

Among the cellular processes linking lipid transfer and metabolism with inter-organelle membrane contact sites, one of the most relevant is macroautophagy (hereafter referred to as autophagy). Autophagy is a catabolic process conserved across eukaryotes that involves the de novo formation of a double-membrane vesicle, the autophagosome [328]. Autophagy ensures cellular homeostasis and plant health, as it not only serves as a stress response but also plays essential roles in development, and organelle turnover. Both bulk and selective forms occur in plants, the latter targeting specific substrates such as protein aggregates or whole organelles, including mitochondria (mitophagy), chloroplasts (chlorophagy), peroxisomes (pexophagy), and the ER (ER-phagy) [329].

Autophagy begins with the emergence of a cup-shaped double membrane, termed the phagophore or isolation membrane, which expands through the addition of lipids and membranes mediated by specific protein machineries, eventually enclosing a portion of cytoplasm. After closure, the autophagosome delivers its cargo to the vacuole, where its outer membrane fuses with the tonoplast. The inner vesicle and its cargo are degraded, and the resulting metabolites are recycled to sustain protein synthesis and energy production [329].

The connection between autophagy and lipid homeostasis in plants operates at several levels. On one hand, autophagy requires lipids for autophagosome biogenesis. On the other, autophagy regulates both lipid droplet formation and degradation [330–332]. These two aspects are addressed separately below.

### *7.1. ER–phagophore contact sites: lipid transfer and autophagosome biogenesis*

Autophagosome formation requires hierarchical interplay between ATG proteins, lipid biosynthesis and transfer. While the protein machinery has been extensively studied, the origin and dynamics of the lipids that sustain autophagy are less well understood. Lipid supply derives from (i) vesicular trafficking, (ii) local synthesis, and (iii) non-vesicular transfer from donor membranes at contact sites [333,334]. PI3P, PI4P, and PE are central to autophagy progression, whereas PA negatively regulates the process in plants [333,335]. In addition, DAG has been postulated to contribute to the autophagosome formation and function as a signaling molecule in plants [333].

Autophagosome formation occurs in two stages: (1) establishment of a distinct membrane identity at the nucleation site, and (2) rapid membrane expansion. In plants, as in mammals and yeast, the ER acts as the main lipid donor during initiation, communicating with the nascent phagophore via ER–phagophore contact sites [336–338]. Nucleation involves the assembly of the ATG1 kinase complex (ULK1 in mammals) at ER subdomains enriched in PI3P and phosphatidylinositol synthase (PIS) [339–341]. ATG9 vesicles function as seeds, recruiting the autophagy machinery and establishing contact sites to initiate lipid transfer from the ER [339,342]. Subsequently, the ATG1 complex activates phosphatidylinositol 3-kinase (PI3K), which synthesizes PI3P at the phagophore [334]. PI3P is essential for recruiting several ATG proteins required for conjugating ATG8 (Fig. 3E)—the signature protein of autophagosomes, known as LC3 in mammals—to PE, in a process termed ATG8/LC3 lipidation. ATG8-PE anchors both the inner and outer phagophore membranes, a step that is essential for phagophore expansion and cargo recognition in mammals, yeast, and plants [334,338].

Thus, nucleation and the establishment of autophagosomal membrane identity critically depend on the localized delivery of PI3P at ER subdomains. In addition, PM-localized PI4Kα1 contributes to autophagy, with a substantial proportion of autophagic structures forming in close proximity to PI4P-enriched PM subdomains [343]. In plants, the ORP2A (Fig. 3E) also plays a pivotal role in this process. The VAP27-1—ORP2A complex forms a tether at ER–phagophore contact sites, where ORP2A interacts with both, the ER-protein VAP27-1 and the autophagosomal protein ATG8e. Loss-of-function mutants in *orp2a* display altered PI3P distribution, impaired autophagosome formation, and abnormal accumulation of the ATG1 kinase complex at ATG8-positive ER-associated structures [106]. Biochemical analysis indicates that ORP2A can bind multiple phosphoinositides, including PI3P [106], and functions as a lipid shuttle transporter that secures the lipid environment required for assembly of the ATG1 initiation complex. Notably, no ORP protein has yet been implicated in autophagy biogenesis in mammals or yeast, highlighting a plant-specific specialization and evolutionary divergence of ORP function.

Once nucleation is established, the process shifts from precision to scale. Phagophore expansion requires substantial lipid input, supplied predominantly by the ER. This is mediated by the bridge-type transporter ATG2 (ATG2A in mammals), which together with ATG18a (WIPI4 in mammals), maintains ER–phagophore tethering during the early stages of autophagosome biogenesis (Fig. 3E) [334]. Beyond its tethering role, in mammals ATG2A exhibits glycerolipid transfer activity in vitro, and this function is sufficient to restore autophagosome formation and the wild-type phenotype in *atg2a/b* double knockout cells [344]. It is therefore hypothesized that ATG2A transfers lipids from the ER to the expanding phagophore [334]. In plants, the ATG2–ATG18a complex is conserved, and their interaction appears to be required for autophagosome closure; however, the lipid transfer capacity and tethering function of ATG2 remain to be demonstrated [345]. Given the conservation of core autophagic machinery across eukaryotes, it is plausible that ATG2 fulfills a similar role in plants, making the functional validation of its activity a research priority.

Complementing this bridge-like lipid transfer system, mammals employ vacuole membrane protein 1 (VMP1) and transmembrane protein 41B (TMEM41B)—two multispanning ER proteins with scramblase activity—that coordinate membrane dynamics during autophagy [346]. Although not tethers themselves, these proteins are proposed to facilitate lipid transfer between ER membrane leaflets, thereby supplying lipids to ATG2A and fueling phagophore growth at ER–phagophore contact sites [347]. VMP1 also interacts with and recruits BECLIN1 (ATG6 in plants), a core component of the PI3K complex, to the phagophore, thereby promoting PI3P synthesis and the recruitment of downstream autophagy factors [348]. In *A. thaliana*, the VMP1 orthologs KMS1 and KMS2 are implicated in ER–Golgi protein transport and leaf senescence but appear not to interact with ATG6 or participate in autophagy [349].

Autophagosome biogenesis is a flexible process that can be initiated from multiple membrane contact sites, integrating signals across organelles. In plants, ER–mitochondria contact sites are essential for mitophagy [224] although, unlike in mammals [350], they have not been demonstrated as sites of autophagosome initiation. Moreover, mammalian *E*-Syts contribute to autophagosome formation by recruiting PI3K complex components and regulating their stability at ER–PM contact sites, a function mediated by E-Syt–VMP1 interaction [351]. Evidence suggests that the plant ortholog SYT1 may also participate in autophagy. In *A. thaliana*, ATG5—a core autophagy factor required for ATG8 lipidation—has been identified as a putative interactor of SYT1, as well as of the Themis-like (TML) subunit of the TPLATE complex [352]. The TPLATE complex, a central component of clathrin-mediated endocytosis [353] has also been implicated in autophagosome biogenesis at ER–PM contact sites. Specifically, its subunit AtEH/Pan1 which interacts with VAP27 to recruit actin and clathrin to form autophagosomes [354]. These findings raise the possibility that SYT1 and the TPLATE complex may functionally cooperate at ER–PM contact sites, coordinating lipid and protein recycling to support autophagosome biogenesis.

Despite the growing understanding of autophagosome biogenesis in plants, several key questions remain unresolved. The precise mechanisms of lipid transfer by ATG2–ATG18a at ER–phagophore contact sites, the contribution of ER–PM contact sites to autophagosome initiation, and the potential roles of plant-specific factors such as ORP2A and SYT1 require further investigation.

### *7.2. Interplay between autophagy and lipid droplets in plant lipid metabolism*

Autophagy and lipid droplets are tightly interconnected in eukaryotes. In plants, as in mammals or yeast, autophagy influences lipid droplet biogenesis and degradation, while lipid droplets lipolysis can provide lipids for autophagosome formation in yeast and mammals [355]. Organisms maintain a basal level of autophagy under favorable conditions and upregulate autophagic activity under stress. In *A. thaliana*, basal autophagy contributes to TAG synthesis and lipid droplet accumulation by promoting organellar membrane turnover, whereas inducible autophagy during stress conditions drives lipid droplet degradation. Disruption of basal autophagy impedes organellar membrane lipid turnover and fatty acid mobilization from membrane lipids to TAG, highlighting a role for the ER glycerolipid biosynthesis pathway rather than the chloroplast pathway in providing lipid precursors [331].

Lipid droplet degradation during dark-induced autophagy and seed germination is mainly mediated by ATG proteins through a process resembling microautophagy, termed microlipophagy [331,356]. Here, lipid droplets are recruited to the vacuole surface and delivered into it via tonoplast invagination. This mechanism, first described in yeast, requires core ATG proteins together with Niemann–Pick type C proteins (Ncr1, Npc2) and PI4-kinases (Stt4, Pik1), and occurs at sterol-rich tonoplast microdomains [357]. In yeast, microlipophagy depends on vacuole–LD contact sites (vCLIP), where the tethering proteins Ldo16 and Ldo45 interact with the vacuolar surface protein Vac8. In addition, Ldo45 recruits the PI transfer protein Pdr16, which associates with lipid droplets. Mutations in Ldo or Vac8—but not in Pdr16—block microlipophagy, underscoring the importance of these contact sites [357,358]. While proteins at LD–organelle interfaces have been identified in plants (see previous section), no plant vCLIP homologs have yet been linked to microlipophagy.

In yeast and mammals, lipid droplet lipolysis also fuels autophagosome formation. Mutations in lipases such as yeast Yeh1/2 or mammalian PNPLA5 impair autophagy [355]. Moreover, yeast ER–LD contact site proteins ICE2 and Ldb16 are required to channel fatty acids for ER membrane synthesis, and their deletion reduces autophagy,

**Table 1**

Plant proteins and complexes with demonstrated or supported localization at contact sites and lipid-related functions.

| Protein or Complex | Protein type | Key lipid substrate(s) | Physiological role | Key Ref. |
|---|---|---|---|---|
| ***ER–PM contact sites*** | | | | |
| SYT1, SYT3 | Tether &Shuttle LTP | DAG/ $PI(4,5)P_2$ | Stress response, membrane repair | [64,77,85] |
| SYT4, SYT5 | Tether & Shuttle LTP | ? | Stress response | [80] |
| CLB1 (SYT7) | Tether & Shuttle LTP | Binds to membrane lipid ceramides | Stress response | [82] |
| DGK1, DGK2 | DAG kinases | DAG | Stress response | [33] |
| ORP2A – VAP27 | Shuttle LTP- Tether | Phytosterols, PI4P | Sterol homeostasis | [16,106,107] |
| ORP3A-VAP27 | Shuttle LTP- Tether | Sitosterol, PI4P | Sterol homeostasis | [17,105] |
| ACD11 | Shuttle LTP | C1P | Sphingolipid homeostasis | [137,138,359] |
| SAC7 | PI4P Phosphatase | PI4P | Maintenance of PI4P gradient | [95,96,100] |
| MCTPs (Plasmodesmata) | Tehters | Bind anionic phospholipids | Signaling and PI metabolism | [103] |
| ***ER–Plastid contact sites*** | | | | |
| TGD1/2/3/4/5 & LptD1 | ABC Transporter | PA | Galactolipid biosynthesis | [164–171] |
| BnCLIP1 | Putative lipase | Multisubstrate | Chloroplast maintenance and lipid mobilization | [172,173] |
| LACS7 / LACS9 - LPCAT | Acyl-CoA synthetases - Acyltransferase | Acyl-CoA activation and lyso-PC acylation | Incorporation of galactolipid precursors | [174–180] |
| ORP2A-VAP27 | Shuttle LTP- Tether | Phytosterols, PI4P, MGDG | Sterol homeostasis | [16,106,107] |
| ALA10/ALI5 complex | Flippase/Chaperone | PC | Galactolipid biosynthesis | [182] |
| SFH5, SFH7 | Shuttle LTP | PA, PC | Glycerolipid biosynthesis | [27,183] |
| ***ER–TGN contact sites*** | | | | |
| SYT6 | Putative shuttle LTP | ? | ? | Preprint [83] |
| ***LD–Peroxisome contact sites*** | | | | |
| PXA1 | Tether/Transporter | Fatty Acyl-CoAs | Fatty acid import for β-oxidation | [313,321] |
| SDP1 and SDP1-LIKE | TAG lipases | TAG | Mobilization of TAG reserves | [312,313] |
| ***ER-Mitochondria contact sites*** | | | | |
| VPS13M1 | Bridge-like LTP | Glycerolipids | Lipid remodeling during phosphate starvation | Preprint [248] |
| ***Mitochondrial inner–outer membrane contacts*** | | | | |
| MTL complex with Mic60–Tom40 | | DGDG import from plastids and PE export | Plastid–mitochondria lipid exchange. | [254–257] |
| ***ER–Autophagosome/phagophore contact sties*** | | | | |
| ORP2A–VAP27 | Shuttle LTP- Tether | PI3P | Autophagosome nucleation | [106] |
| ATG2 | Bridge-like LTP | Glycerolipids | Phagophore expansion | [344,345] |

Abbreviations: C1P, Ceramide-1-phosphate; DAG, diacylglycerol; DGDG, digalactosyldiacylglycerol; ER, endoplasmic reticulum; LD, lipid droplet; LTP, lipid transfer protein; MGDG, monogalactosyldiacylglycerol; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PI3P, phosphatidylinositol-3-phosphate; PI4P, phosphatidylinositol-4-phosphate; $PI(4,5)P_2$, phosphatidylinositol-4,5-bisphosphate; PM, plasma membrane; TAG, triacylglycerol; TGN, trans-Golgi network.

although whether this specifically supports autophagosomal membrane lipids remains unresolved [355]. To date, no studies in plants have addressed whether lipid droplet lipolysis contributes to autophagosome biogenesis. Elucidating this potential interplay, and identifying the molecular players involved, remains an unresolved question in plant lipid and autophagy research.

## 8. Conclusions and future perspectives

Plant organelles are dynamically integrated through membrane contact sites, which mediate lipid exchange and in situ lipid metabolism, processes essential for membrane identity, signaling, and adaptation. A unifying theme emerging from recent work is the central role of the ER as a lipid factory and distribution hub, and the existence of a continuum of lipid transport mechanisms—from precision-regulated shuttle transfer that enforces local identity and signaling, to high-capacity bridge-like transfer that fuels rapid membrane biogenesis and remodeling. These advances underscore the evolutionary specialization of the plant contactome, which has been shaped by photosynthesis, the cell wall, and sessile life history.

To date, only a handful of lipid transfer proteins and lipid-modifying enzymes localized at membrane contact sites have been experimentally identified and functionally characterized in plants (Table 1). Notably, it is also possible that lipid transfer is not exclusively mediated by dedicated transport proteins: some enzymes involved in lipid metabolism may localize to contact sites and contribute directly to lipid transfer, a possibility that remains largely unexplored. Thus, a major priority is the biochemical identification of the missing transporters and tethers that execute lipid flux at key junctions. Open questions include the identities of plant PI-transfer proteins at the ER–PM interface (for example, SEC14L-PITP paralogs that might functionally parallel mammalian Nir2/TMEM24), the identification of proteins mediating sterol and sphingolipid exchange at the PM, the specific lipids shuttled at ER–-plastid junctions that sustain galactolipid biogenesis, or some direct *in planta* evidence that AtVPS13M1 or related paralogs perform lipid transfer at ER–mitochondria contacts. Relatedly, the roles of plant FYVE-domain proteins (such as FREE1) in mediating ER–endosome contacts and lipid exchange deserve focused attention. Addressing these issues will require integrated approaches: comparative genomics, contact-site proteomics, systematic genetic screens, biochemical co-purification of membrane fractions, or in vitro lipid-transfer assays using recombinant proteins and defined liposomes.

Understanding how lipid transfer proteins are regulated and coordinated at contact sites represents a second challenge ahead. Beyond identifying proteins, we must understand how they function in a coordinated manner. Many fundamental questions about the regulation and mechanism of lipid transfer proteins remain unresolved: how lipid transfer activity is regulated, since $Ca^{2+}$-dependency is established for SYTs but regulatory inputs for ORPs, VPS13, and others are largely unknown; how post-translational modifications and protein–protein interactions shape their activity; how cells switch between shuttle and bridge transport modes, potentially under the control of master signaling pathways such as stress hormones; and how lipid-modifying enzymes and lipid transfer proteins act as integrated assembly lines or metabolons at contact sites to enable in situ modification of lipids during transfer. Moreover, the structural basis of multi-organelle junctions such as the ER-nest remains to be elucidated, raising important questions about how tripartite contact sites are assembled and stabilized to channel metabolic flux efficiently.

Quantification of lipid flux across contact sites is another pressing challenge, as this field is currently largely descriptive. The next great leap will be to measure actual transfer rates in vivo. What are the molecular fluxes (molecules/s) through a SYT1 shuttle compared to a VPS13 bridge? How do these rates compare to vesicular trafficking? To answer these questions, new technologies will be needed. A recent breakthrough in animal cells, combining time-resolved fluorescence imaging of bifunctional lipid probes with ultra-high-resolution mass spectrometry and mathematical modeling, have provided a roadmap for measuring inter-organelle lipid flux [13] and exemplifies the kind of quantitative approach needed in the plant field.

To truly understand the contactome as an integrated network, research must move beyond isolated contacts toward a system-level view. This requires the integration of spatially resolved proteomics, combined with super-resolution imaging (STED, PALM), cryo-electron tomography, or immuno-TEM to visualize contact site architecture in situ. Recently developed optogenetic tools, such as LiMETER [360], will allow functional interrogation of contact-site dynamics in living cells. Such approaches will illuminate how the contactome remodels in response to environmental stresses such as drought, pathogen attack, or nutrient deprivation, and how cells rewire lipid trafficking networks to adapt to changing conditions.

Finally, an emerging challenge is linking the contactome to plant development and morphogenesis, an area that has received less attention than metabolism and stress. Processes such as lipid delivery during cytokinesis for cell-plate formation or the regulation of localized lipid composition essential for polar cell growth almost certainly depend on precise coordination at contact sites. Yet, direct evidence is limited. Exploring these functions will broaden the scope of the field and significantly enhance the impact of future research on plant lipid metabolism.

Unraveling these complex mechanisms will be critical for understanding how plants coordinate lipid metabolism with dynamic membrane signaling. This will not only refine fundamental principles of plant cell biology but also provide translational opportunities for engineering stress resilience, improving photosynthetic efficiency, and rationally redesigning lipid metabolism in crops.

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## CRediT authorship contribution statement

**Carolina Huercano:** Writing – review & editing, Writing – original draft, Conceptualization. **Miriam Moya-Barrientos:** Writing – review & editing, Writing – original draft, Conceptualization. **Oliver Cuevas:** Writing – review & editing, Writing – original draft. **Carlos Cardenas:** Writing – review & editing, Writing – original draft. **Joaquín J. Salas:** Writing – review & editing. **Victoria Sanchez-Vera:** Writing – review & editing, Writing – original draft. **Noemi Ruiz-Lopez:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

## Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT, Elicit, Google Gemini and Perplexity in order to improve the readability and language of the manuscript and search for articles published in the topic. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Data availability

No data was used for the research described in the article.

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## Glossary

*'Bridge-like' model (lipid transport):* A mode of non-vesicular lipid transfer in which large proteins form a continuous hydrophobic conduit spanning the intermembrane gap. These proteins contain lipid-filled grooves or tunnels that allow bulk lipid flow between organelles.

*'Shuttle' model (lipid transport):* A mechanism of non-vesicular lipid exchange in which lipid transfer proteins bind one or a few lipid molecules at a time and shuttle them across the cytosolic gap between adjacent membranes. Shuttle-type lipid transfer proteins can exchange specific lipid species between bilayers, sometimes driving transport against concentration gradients through counter-exchange mechanisms.

*Fatty acid $\beta$-oxidation:* A catabolic pathway occurring in peroxisomes and mitochondria where fatty acids are sequentially degraded to produce acetyl-CoA, NADH, and $FADH_2$. Acetyl-CoA feeds the citric acid cycle, while NADH and $FADH_2$ drive the electron transport chain to generate ATP. It is the principal route for energy release from fatty acids.

*FFAT (Two Phenylalanines in an Acidic Tract):* A short peptide motif defined by two conserved phenylalanine residues within an acidic sequence context. It mediates interaction with VAP (VAMP-associated protein) at the ER, thereby tethering partner organelles and facilitating lipid exchange at membrane contact sites.

*Galactolipid biosynthesis:* The plastid-localized pathway that produces the galactoglycerolipids monogalactosyldiacylglycerol (MGDG) and digalactosyldiacylglycerol (DGDG). These galactolipids constitute the major structural components of chloroplast thylakoid membranes and dominate photosynthetic membrane lipid composition.

*Lipid transfer protein (LTP):* A protein that mediates lipid exchange between membranes, typically at membrane contact sites. LTPs contain hydrophobic cavities, pockets, or channels that accommodate specific lipid molecules for transfer across the cytosolic gap.

*Membrane contact site (MCS):* A specialized region where the membranes of two organelles are closely apposed (typically 10–80 nm apart) but do not fuse. MCSs are stabilized by tethering proteins and/or lipid interactions and mediate exchange of lipids, ions, and metabolites.

*Metabolon:* A supramolecular complex formed by sequential enzymes of a metabolic pathway that are physically associated in close proximity. This organization enhances pathway efficiency, minimizes diffusion of intermediates, and allows tight regulation of metabolic flux.

*Non-vesicular lipid transport:* The transfer of lipids between membranes independent of vesicular trafficking. It is mediated by soluble lipid carriers or by proteinaceous bridges that connect membranes at contact sites.

*Organelle contactome:* The integrated and dynamic network of all membrane contact sites within a cell. The contactome is highly plastic and remodels in response to metabolic and environmental cues, thereby coordinating inter-organelle communication.

*Pleckstrin Homology (PH) domain:* A conserved structural module found in many signaling and cytoskeletal proteins. PH domains typically bind phosphoinositides (e.g., PI(4,5)$P_2$), targeting proteins to specific membrane subdomains and regulating signal transduction.

*Phosphatidylinositol cycle:* A lipid signaling and recycling pathway centered at ER–PM contact sites. In plants, agonist-activated phospholipase C at the plasma membrane hydrolyzes phosphoinositides to generate DAG and inositol phosphates, triggering $Ca^{2+}$-dependent signaling. The DAG is then returned to the ER, where it is sequentially converted to PA and PI, ultimately regenerating PI(4,5)$P_2$.

*Plasmodesmata (PD):* Plant-specific cytoplasmic channels that traverse cell walls, enabling direct intercellular exchange of metabolites, ions, signaling molecules, proteins, and RNAs. They are essential for cell-to-cell communication and developmental coordination.