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## Chapter 4

### Non-vesicular glycerolipids transport in plant cells

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#### Abstract

In Eukaryotic cells, organelles are delineated by one or several membranes that are composed of a specific assembly of lipids and proteins ensuring the identity of each cell compartment and regulating their biogenesis and function. Lipids regulate many aspects of cell biology including vesicular trafficking, protein targeting, programmed cell death or signaling. They also play key roles in response to stress, which is particularly important for organisms such as plants that constantly cope with a multitude of environmental variations. Membranes are mainly composed of glycerolipids, sterols and sphingolipids. Lipid precursors are primarily synthesized in plastids and in the endoplasmic reticulum. Then, they have to be specifically directed to other cell compartments where they can be modified and transported to other organelles to regulate membrane biogenesis and function. Thus, lipid transfer is a key process involved in the maintenance of membrane homeostasis, in particular in stress conditions. Lipid exchanges between organelles can rely on vesicular or non-vesicular transport. Whereas vesicular transport concerns mainly organelles connected to the endomembrane system, such as the Golgi, vacuoles or the plasma membrane, non-vesicular lipid trafficking concerns virtually all organelles. This lipid transfer mechanism is thought to occur at membrane contact sites, corresponding to specific cell structures formed by the close apposition of two membranes at a distance  $\leq 30\text{nm}$ . In this chapter, we will summarize our current knowledge about the mechanisms involved in non-vesicular lipid transport in plant cells, with a particular focus on glycerolipids, the main components of organelle membranes.

Key words: Non-vesicular lipid transport, Membrane contact sites, Membrane biogenesis, Lipid transfer proteins, Glycerolipids, Plants.

Running title: Non-vesicular lipid transport in plant cells

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# 1 Introduction

## 1.1 Glycerolipid synthesis in plant cells

Glycerolipids are composed of a glycerol backbone esterified with two fatty acids (FAs) in position *sn-1* and *sn-2* (Figure 1A). FAs are defined by the length of their carbon chain and the number of double bonds (or unsaturations). In *Arabidopsis thaliana*, glycerolipid acyl-chains are mainly composed of 16 or 18 carbons (C16, C18) with up to three unsaturations (C16:0 to C16:3 and C18:0 to C18:3) (Li-Beisson et al., 2013). The nature of the polar head associated to the position *sn-3* will define the class of the glycerolipid molecule. Three main classes are found in plants: 1) the phospholipids, containing a phosphate (Pi) moiety, 2) the galactoglycerolipids, containing one or two galactose residues for the monogalactosyldiacylglycerol (MGDG) or the digalactosyldiacylglycerol (DGDG) respectively, and 3) the sulpholipid sulphoquinovosyldiacylglycerol (SQDG), containing a sulphoquinovosyl group in its polar head (Figure 1B). Galactoglycerolipids and SQDG are the main constituents of plastid membranes, where they play a major structural and functional role in photosynthesis, whereas phospholipids are the main glycerolipids found in extra-plastidial membranes. Enzymes involved in the synthesis of galactoglycerolipids, SQDG and of plastidial phosphatidylglycerol (PG) are localized in plastid envelopes (Boudière et al., 2014; Li-Beisson et al., 2013). Enzymes involved in phospholipids synthesis are mainly located in the endoplasmic reticulum (ER) and some are also found in mitochondria or in the endomembrane system (Li-Beisson et al., 2013; Michaud et al., 2017). In plants, FA biosynthesis occurs in the plastid stroma and gives rise to C16:0-acyl carrier protein (ACP) and C18:1-ACP (Li et al., 2016). These acyl-chains can then be directly used to feed the synthesis of plastidial lipids by the so-called Prokaryotic pathway or they can be exported in the cytosol and integrated into glycerolipids in the ER by the so-called Eukaryotic pathway (LaBrant et al., 2018; Li-Beisson et al., 2013). These two pathways lead to the biogenesis of phosphatidic acid (PA) and diacylglycerol (DAG), two precursor molecules that will be used to synthesize the whole set of plant glycerolipids (Figure 1). Importantly, after their synthesis, glycerolipid molecules can be subjected to a wide variety of modifications, such as acyl-chain remodeling or polar head modifications, combined to their transport to different cell compartments or translocation from one membrane leaflet to another. The vast variety of pathways involved in these processes highlights the complexity of maintaining membrane lipid homeostasis.

## 1.2 Non-vesicular glycerolipid transport in plant cells

### 1.2.1 Where does non-vesicular glycerolipid transport occur in plant cells?

Lipid transport can be mediated by vesicular or non-vesicular pathways. The vesicular pathway involves the transport of lipids, as well as proteins and soluble molecules, in vesicles that will emerge from a donor organelle, be transported through the cytosol and finally fuse with the acceptor organelle to deliver their content. This trafficking route concerns organelles connected to the endomembrane system, such as the ER, the vacuole, the Golgi or the plasma membrane (PM) (Cevher-Keskin, 2020). In plants, vesicular transport also occurs in plastid stroma where this process is involved in the synthesis of thylakoids (Lindquist & Aronsson, 2018). Non-vesicular lipid transport corresponds to the direct transfer of lipid molecules from one membrane to another. This process is involved in the biogenesis of virtually all organelles, but those not connected to the vesicular transport pathway, like mitochondria or plastids, are completely dependent on this lipid transport route to ensure their biogenesis and function (Bayer et al., 2017; Hurlock et al., 2014; LaBrant et al., 2018; Michaud et al., 2017). Non-vesicular lipid transport is thought to occur at membrane contact sites (MCSs), corresponding to particular cell structures formed by the close apposition of two membranes at a distance  $\leq 30\text{nm}$  (Michaud & Jouhet, 2019; Petit et al., 2019; Scorrano et al., 2019). The short distance between the two membranes at MCSs is supposed to decrease the soluble

interface that amphiphilic lipid molecules have to cross from the donor to the acceptor membranes. Three types of proteins can be found at MCSs: 1) the tethers, which are proteins able to bridge and maintain the two membranes in close apposition, 2) the effectors, corresponding to proteins providing functionality to the MCSs, and 3) proteins that share both functions (Bohnert & Schuldiner, 2018; Prinz et al., 2019; Scorrano et al., 2019). Beside lipid transport, MCSs play essential roles in many cellular processes including ion exchanges, programmed cell death, organelle division, and appear now as cellular hubs for the regulation of organelle biogenesis and function and cell signaling (Michaud & Jouhet, 2019; Prinz et al., 2019; Scorrano et al., 2019). Contact sites between many organelles have been observed in plants, but we are just starting to understand their role and importance. Plant MCSs are highly dynamic and regulated during development and in response to many biotic and abiotic stresses (Liu & Li, 2019; Mathur, 2020; Michaud & Jouhet, 2019). In this chapter, we will mainly focus on their role in plant lipid transport. For recent reviews about plant MCSs, see (Liu & Li, 2019; Michaud & Jouhet, 2019; Mueller-Schuessele & Michaud, 2018; Perez-Sancho et al., 2015; Petit et al., 2019).

In plants, lipid transport could virtually occur between all organelles. However, the currently available information about the transported molecules and the mechanisms involved are scarce. By analogy to yeast and animal systems, it can be suspected that huge lipid transport between the ER and mitochondria and the ER and the PM occurs, but direct proofs of such transport and the nature of the transported lipids are still missing (Michaud et al., 2017; Perez-Sancho et al., 2016; Petrunaro & Kornmann, 2019; Saheki & De Camilli, 2017a). The most investigated non-vesicular lipid trafficking route in plants corresponds to the ER to chloroplast transport of lipid precursors to synthesize plastid lipids. As described above, plastids have the ability to synthesize *de novo* lipid precursors by the Prokaryotic pathway and to import precursors synthesized in the ER from the Eukaryotic pathway. Due to the specificity of the plastidial and ER *sn*-2 acyltransferases, glycerolipids arising from both pathways have an acyl-chain signature at the *sn*-2 position corresponding to a C16 or a C18 for the glycerolipids arising from the Prokaryotic or the Eukaryotic pathways respectively (Figure 1A) (Hurlock et al., 2014; LaBrant et al., 2018). In *A. thaliana*, around 50% of plastidial lipids come from the Eukaryotic pathway whereas in other plants, like grasses, they almost all arise from this pathway (Browse et al., 1986; Mongrand et al., 1998). Thus, an extensive transfer of lipids from the ER to plastids is required to sustain chloroplast biogenesis. The identity of the transported precursor molecule is still under debate, but it is now widely accepted that different precursors, such as phosphatidylcholine (PC), lyso-PC (*i.e.* a PC molecule with one acyl-chain), PA or DAG, could be imported into plastids by several co-existing pathways.

The particularity of plant organisms is their ability to adapt to a wide variety of stresses including pathogen attacks, nutrient starvation, extreme temperatures, high light exposure or drought. The modification of plant lipid composition is a widespread phenomenon involved in cell adaptation to stress (Liu & Li, 2019; Liu et al., 2019; Michaud & Jouhet, 2019; Moellering & Benning, 2011). The modification of the plant lipidome can play a role in signal transduction by the generation of lipid signaling molecules such as PA, lyso-lipids, free FAs or phosphatidylinositide phosphates (PIPs) (Hou et al., 2016). It can also play a direct role in the adaptation of plant cells to environmental changes, for instance by modifying membrane fluidity during cold or heat stress or by triggering energy storage by the accumulation of triacylglycerols (TAGs) into lipid droplets (LDs) in response to nitrogen starvation (Liu et al., 2019; Meï et al., 2015; Upchurch, 2008). The best-studied lipid remodeling process occurs in response to phosphate (Pi) starvation, a frequent nutrient stress encountered by plants in nature. Phospholipids retain up to one third of the intracellular Pi content and constitute an important Pi reserve (Poirier et al., 1991). During Pi starvation, plants partially degrade their phospholipids to remobilize intracellular Pi (Plaxton & Tran, 2011; Poirier et al., 1991).

To maintain membrane integrity, the degraded phospholipids are replaced by DGDG (Hartel et al., 2001; Jouhet et al., 2003; Tjellström et al., 2008). Since DGDG is exclusively synthesized in plastids, a massive DGDG export from this organelle to extra-plastidial membranes like vacuole, mitochondria and PM takes place (Andersson et al., 2005; Jouhet et al., 2004). The transfer of DGDG from plastids to mitochondria is thought to occur by non-vesicular routes at MCSs between the two organelles as their number significantly increases in response to Pi starvation (Jouhet et al., 2004). However, the mechanisms involved in DGDG transport from plastids to vacuoles and PM (*i.e.* vesicular or non-vesicular) are still unknown.

### 1.2.2 How does non-vesicular glycerolipid transport occur in plant cells?

The non-vesicular transport of lipids can be divided in three steps: 1) the desorption of the lipid from the donor membrane, 2) its transport through the cytosol and 3) its insertion into the acceptor membrane. The limiting step is the desorption of the lipid from the donor membrane because of the high-energy barrier linked to the extrusion of amphipathic molecules from their hydrophobic environment (Sommerharju, 2015). Different mechanisms have been proposed to mediate non-vesicular lipid transport in cells. Spontaneous transport of glycerolipids can occur (Figure 2A), but this process is likely irrelevant in the context of cell division as the half time of spontaneous PC transport *in vitro* ranges from several hours to days (Sommerharju, 2015). Obviously, many factors can influence the rate of spontaneous transport of glycerolipids, including the composition of the donor membrane and the hydrophobicity of the transported molecules (length and unsaturation level of the acyl-chains). For instance, the *in vitro* spontaneous transfer rate of lysolipids significantly decreases compared to glycerolipids, ranging from seconds to minutes (Sommerharju, 2015). It has also been proposed that MCSs might form microdomains with a specific lipid and protein composition favoring non-vesicular lipid transport (Gaigg et al., 1995; Pichler et al., 2001; Sommerharju, 2015), but this remains to be determined. *In vivo*, many proteins, such as lipid transfer proteins (LTPs) (Figure 2B-E), as well as multi-subunit complexes that can cross at least two membranes (Figure 2F), are involved in non-vesicular lipid transport. In addition, some membrane proteins can act in concert with LTPs to promote membrane lipid desorption or insertion (Figure 2G). In this chapter, these mechanisms will be discussed in plants. As our current knowledge is scarce, we will rely on the lipid transfer processes described in other organisms to draw a more global picture of the putative mechanisms involved in non-vesicular glycerolipid transport in plant cells.

(Insert Figure 2 here)

## 2 Lipid transport mediated by LTPs

LTPs can be divided into different families depending on their structure and mechanism of lipid transport, but they all share common features: 1) they possess a soluble domain with a hydrophobic cavity accommodating one or several lipid molecules, favoring the transport of lipids through soluble compartments, and 2) they are able to significantly increase the rate of glycerolipid transfer between membranes (Reinisch & Prinz, 2021; Sommerharju, 2015; Wong et al., 2019). Some LTPs have also been proposed to directly facilitate membrane lipid desorption or to associate to membrane proteins favoring lipid extrusion (Lipp et al., 2020; Reinisch & Prinz, 2021; Wong et al., 2019). Two main mechanisms have been proposed for LTPs: 1) the shuttle mechanism, where the lipid-binding domain of LTPs is able to diffuse through the soluble compartment to shuttle lipids from one membrane to another (Figure 2B-D) and 2) the bridge-like mechanism in which LTPs are able to form hydrophobic tunnels contacting simultaneously two membranes between which lipids will be transported (Figure 2E) (Reinisch & Prinz, 2021; Wong et al., 2019). LTPs can be soluble and transiently associated to membranes *via* protein-lipid or protein-protein interaction (Figure 2B) or anchored to membranes by

transmembrane (TM) domains (Figure 2C). Indeed, as further described in this chapter, the lipid-binding domain of LTPs is often associated to additional domains, the most frequent being the pleckstrin-homology (PH) domain, which specifically binds to PIPs, and the C2 domains that can bind a wider range of membrane lipids. These additional domains allow LTPs targeting to particular organelles or MCSs (Reinisch & Prinz, 2021; Wong et al., 2019). Furthermore, some LTPs are able to simultaneously bind two membranes and are able to act as lipid transporters and membrane tethers at MCSs (Figure 2D). In plants, a few LTPs has been characterized until now but they are involved in a wide variety of cellular processes beside lipid transport such as lipid signaling, plant resistance to pathogens, adaptation to many abiotic stresses or regulation of gene expression (Table 1).

## 2.1 The SMP family.

The SMP (synaptotagmin-like mitochondrial-lipid binding protein) domain is a lipid binding/transport domain belonging to the TULIPs (tubular lipid binding proteins) superfamily of LTPs (Kopec et al., 2010; Wong & Levine, 2017). SMP domain-containing proteins are evolutionary conserved among Eukaryotes (Craxton, 2004; Lee and Hong, 2006). This family has been mostly studied in yeast and mammals and shown to be located at various MCSs: 1) at ER-PM MCSs, for the Extended synaptotagmins (E-Syts), also called Tricalbins in yeast (Perez-Sancho et al., 2015; Saheki & De Camilli, 2017b), 2) at ER-mitochondria MCSs, for the ERMES (ER-mitochondria encounter structure) complex subunits in yeast and the PDZD8 protein in mammals (Hirabayashi et al., 2017; Kornmann et al., 2009), 3) at ER-Golgi MCSs for Nvj2 in yeast (Liu et al., 2017) and 4) at the ER-endosomes MCSs for PDZD8 (Elbaz-Alon et al., 2020; Shirane et al., 2020). The SMP proteins are mostly predicted to be anchored to membranes by one TM segment linked to the SMP domain by a flexible linker (Lee & Hong, 2006; Saheki & De Camilli, 2017b). Other domains can also be associated, as exemplified by C2 domains located in E-Syts allowing the binding of the protein to a second membrane enriched in PIPs (see below). Cristal structures of the SMP domains show that they fold into a  $\beta$ -barrel structure oligomerizing to form hydrophobic tunnels that can accommodate phospholipid molecules (Jeong et al., 2017; Saheki & De Camilli, 2017b; Schauder et al., 2014). SMP domains are able to form homodimers or heteromultimers (AhYoung et al., 2015; Schauder et al., 2014). Analyses of lipids bound to purified proteins as well as *in vitro* transfer assays support the role of SMP proteins in phospholipid transport between membranes at MCSs, independently of the polar head, suggesting that SMP proteins are non-specific glycerolipid transporters (AhYoung et al., 2015; Jeong et al., 2017; Saheki et al., 2016). The flexible linkers located between the TM and the SMP domain of these proteins allow the movement of the lipid binding domain in the cytosol to shuttle lipids from one membrane to another in an ATP-independent manner (Figure 2D) (Jeong et al., 2017; Schauder et al., 2014). By searching in the literature and in domain databases, 13 proteins containing a SMP domain can be identified in *A. thaliana* (Table 2) (Ishikawa et al., 2020; Perez-Sancho et al., 2016). Seven show a domain organization similar to E-Syts and two to Nvj2 proteins.

(Insert Table 2 here)

### 2.1.1 E-Syts

E-Syts contain a TM domain anchoring the protein in the ER, and one or several C2 domains located in the cytosol (Perez-Sancho et al., 2016; Saheki & De Camilli, 2017b). C2 domains are able to bind PIPs-enriched PM in a  $\text{Ca}^{2+}$ -dependent manner, allowing the localization of E-Syts at ER-PM MCSs (Figure 2D). At this junction, E-Syts play a dual role as tethers and lipid transporters (Jeyasimman & Saheki, 2020; Saheki et al., 2016). Whereas yeast and human genomes contain three E-Syt genes (Reinisch & De Camilli, 2016), this family is expanded in plants, with seven members

found in *A. thaliana* genome (Table 2) (Ishikawa et al., 2020). Among this family, Syt1, Syt3, Syt5 and Syt7 (also called AtCLB1) are enriched at ER-PM MCSs and are ubiquitously expressed at a high level (de Silva et al., 2011; Ishikawa et al., 2020; Lee et al., 2020). Intriguingly, Syt7, which binds ceramides, was also observed in the nuclear envelope of root tip cells. Syt7 associates to AtTASH1 promoter to negatively regulate the expression of this gene involved in the synthesis of triterpenoids required for root development (de Silva et al., 2011). The regulation of the localization of this membrane protein to either ER-PM MCSs or the nucleus remains to be investigated. Syt2 is highly expressed in pollen and localized in Golgi and PM (Wang et al., 2015; Zhang et al., 2011). Syt2 is involved in non-conventional secretion pathways and plays a role in pollen development and pollen tube elongation (Wang et al., 2015; Zhang et al., 2011). These results show that, in contrast to yeast and mammals, plant E-Syts have a broader subcellular localization and could be involved in the regulation of a wider range of cellular processes besides ER-PM tethering and lipid transport, including gene expression regulation.

The most characterized E-Syt in plants is Syt1 in *A. thaliana*. Syt1 is anchored in the ER by its N-terminal TM segment and is able to bind negatively charged lipids in the PM *via* the two C2 domains protruding in the cytosol (Figure 3A) (Lee et al., 2020; Perez-Sancho et al., 2015; Ruiz-Lopez et al., 2020; Schapire et al., 2008; Yamazaki et al., 2008, 2010). Whether the PM binding is Ca<sup>2+</sup> dependent or not is still a matter of debate (Perez-Sancho et al., 2015; Ruiz-Lopez et al., 2020; Schapire et al., 2008). The localization of Syt1 to ER-PM MCSs also requires VST (VAP-related suppressor of TMM) proteins, which are peripheral PM proteins implicated in stomatal development (Ho et al., 2016). Syt1 is involved in many aspects of plant development and biotic and abiotic stress response. Indeed, ER-PM proximity is highly regulated during plant development and in response to different stresses exerting huge constraints on the PM, such as high salinity, osmotic stress, mechanical stress or freezing (Ho et al., 2016; Lee et al., 2019; Lee et al., 2020; McFarlane et al., 2017; Perez-Sancho et al., 2015). In such situations, increasing of ER-PM MCSs is thought to stabilize the PM and to favor its recovery after damages. In accordance with the key role of Syt1 in these processes, 1) Syt1 is overexpressed during cold acclimation or mechanical stress, 2) *syt1* mutants are sensitive to freezing, high NaCl concentration, drought, osmotic or mechanical stress and 3) a decrease of PM integrity is observed in *syt1* mutants (Perez-Sancho et al., 2015; Ruiz-Lopez et al., 2020; Schapire et al., 2008; Yamazaki et al., 2008). Syt1 is also located at ER-PM MCSs close to plasmodesmata (PD) entries. PDs are channels crossing the plant cell wall, ensuring a continuity of PM, ER and cytosol between plant cells and allowing cell-to-cell communication (Petit et al., 2019). In PDs, ER diameter is reduced and ER-PM MCSs mediated by Syt1, as well as by Syt5 and 7, are suspected to play a role in ER constriction to enter and cross PDs (Ishikawa et al., 2020). Contrary to what is observed in the case of abiotic stress, *syt1* mutants exhibit a higher resistance to fungi and viral infection, notably by reducing pathogen entry into cells or limiting cell-to-cell transmission of viral particles through PDs (Ishikawa et al., 2020; Kim et al., 2016; Levy et al., 2015). Syt1 is able to interact with three other E-Syts, Syt3, Syt5 and Syt7, suggesting it could also form heteromultimeric complexes at ER-PM MCSs, maybe to promote lipid transfer as in mammals (Ishikawa et al., 2020; Lee et al., 2020; Ruiz-Lopez et al., 2020). Recently, it has been shown that Syt3 has a redundant function with Syt1. Both proteins are involved in ER-PM MCSs formation and are more abundant in these sites during cold stress (Ruiz-Lopez et al., 2020). Interestingly, lipidomic analyses of the double *syt1/3* mutant under cold stress show no changes in the whole leaf lipidome but a specific accumulation of DAG and PC in PM fraction, suggesting that DAG clearance from PM is impaired in the double mutant (Ruiz-Lopez et al., 2020). DAG accumulation in PM could be responsible for the cold hypersensitivity of the *syt1/3* mutant by altering PM integrity. In addition, Syt1 co-purifies with DAG (Ruiz-Lopez et al., 2020), further supporting a role of Syt1, and likely Syt3, in DAG transport at

ER-PM MCSs during cold stress (Figure 3A). This first study confirms that, like in yeast and metazoans, E-Syts are involved in both ER-PM tethering and lipid transport, opening important perspectives about the role of these proteins in PM biogenesis and response to stress. Interestingly, five mRNA splice variants were detected for Syt3 (Ruiz-Lopez et al., 2020), increasing the putative number of Syts present in plant cells and the functions they can perform.

### 2.1.2 Other SMP-domain containing proteins.

The localization and role of the six other *A. thaliana* SMP domain-containing proteins are currently unknown. At1g73200 and At1g17820 have a similar domain organization than yeast Nvj2 with a TM domain separated of the SMP domain by a PH domain (Table 2). Nvj2 is involved in the formation of ER-Golgi contacts and ceramide transport to Golgi to alleviate the ER cytotoxicity linked to ceramide accumulation (Liu et al., 2017). At1g73200 is able to restore ceramide transport and ER-Golgi tethering in the yeast  $\Delta nvj2$  mutant, suggesting that At1g73200 and At1g17820 might be Nvj2 orthologs (Liu et al., 2017). The At1g50260 and At3g19830 proteins present an unusual domain organization with four predicted TM domains flanking a SMP and a C2 domain (Table 2). This organization seems to be found only in plants (Lee & Hong, 2006). The At3g60950 and At3g61030 proteins are the only *A. thaliana* SMP proteins that do not contain a TM domain (Table 2). The SMP domain is associated to a C2 and an endonuclease/exonuclease/phosphatase super family domain that was not found associated to SMP domain in other organisms. No putative orthologs of the ERMES complex subunits or PDZD8, involved in ER-mitochondria and ER-endosomes lipid transport in yeast and mammals respectively, were found in *A. thaliana* genome.

## 2.2 The StARkin super-family

The StARkin (relatives (kin) of steroidogenic acute regulatory protein (StAR)) is a large superfamily of LTPs that gather families sharing a common lipid binding/transfer domain folding despite a low sequence conservation (Hanada, 2018; Wong & Levine, 2016). The StARkin lipid binding/transfer domain is composed of a curved  $\beta$ -sheet containing seven strands and of  $\alpha$ -helices that form a hydrophobic cavity accommodating amphiphilic molecules (Wong & Levine, 2016). StARkin super family includes the StARTs (StAR related transfers), the LAMs (lipid transfer at membrane contact sites), the PITPs (phosphoinositol (PI) transfer proteins), the Ups/PRELI and the Bet-V1 protein family. Bet-V1 (also called PR10) proteins are plant-specific. They are able to bind a wide variety of amphiphathic molecules and are involved in the synthesis of many compounds such as flavonoids, alkaloids, sporopollenin or polyphenolics, for instance in response to pathogen infection. As their main substrates are not glycerolipids, this family will not be further described in this chapter (for a recent review about Bet\_V1 proteins, see (Morris et al., 2021)). PITPs with a StARkin domain play a role in the transport of PI, PC, PA or sphingolipids in different cell compartments and are involved in many cellular processes such as PIPs signaling, vesicular trafficking or sphingolipid synthesis. This family is mainly present in metazoans but is not conserved either in plants or in yeasts and thus will not be further discussed in this chapter (for recent reviews, see (Grabon et al., 2019; Selitrennik & Lev, 2016)).

### 2.2.1 The LAM family

LAM proteins are lipid transporters located at MCSs and conserved throughout the Eukaryotic lineage. All the LAM proteins studied until now are sterol transporters (Khafif et al., 2014; Wong & Levine, 2016). These proteins have a conserved organization with 1) a GRAM (glucosyltransferases, Rab-like GTPase activators and myotubularins) domain, corresponding to a PH-like domain involved in protein/protein or protein/lipid interactions, 2) one or two VAST (VAD1



analog of StAR-related lipid transfer) domains, involved in lipid binding and transport and 3) a C-terminal TM domain (Hanada, 2018; Wong & Levine, 2016). The three human LAMs, as well as the yeast Lam1-4 proteins are located at ER-PM MCSs, whereas Lam5 and Lam6 are detected at multiple MCSs in yeast (Elbaz-Alon et al., 2015; Gatta et al., 2015; Murley et al., 2015; Sandhu et al., 2018). They are anchored in the ER by their TM domain but the domains and mechanisms involved in their association with a second organelle remain elusive. Lam6 associates to mitochondria and vacuole through interactions with the protein import receptors Tom70/71 and Vac8 respectively (Murley et al., 2015). *In vitro*, the VASt domains of Lam2/4 is able to bind phosphatidylserine (PS)-containing liposomes. The transport efficiency of the VASt domain of GRAMD1 proteins is enhanced by the addition of anionic lipids (PS or PIPs) in the acceptor liposome (Horenkamp et al., 2018; Tong et al., 2018), suggesting that the anchoring to a second membrane could also be achieved by interactions of LAMs with lipids. Structural analyses of the VASt domain of several LAM proteins show it is monomeric and folds into a hydrophobic pocket accommodating one sterol molecule (Gatta et al., 2018; Horenkamp et al., 2018). *In vitro*, the VASt domain of most of the LAMs is able to bind and transport sterols between membranes in an ATP-independent manner (Gatta et al., 2015, 2018; Horenkamp et al., 2018; Murley et al., 2015). This transport activity was also confirmed *in vivo*, where LAM proteins are able to shuttle sterols at ER-PM or ER-vacuole junctions (Gatta et al., 2015; Murley et al., 2017; Sandhu et al., 2018). In yeast, Lam2/4 and Lam6 trigger the formation of sterol-enriched microdomains in the PM and in the vacuole respectively, playing a role in signaling during stress response (Murley et al., 2015, 2017).

*A. thaliana* genome contains four putative LAM proteins (Khafif et al., 2014; Wong & Levine, 2016). Besides VAD1, plant LAMs have an unusual domain organization compared to yeast and mammals with the presence of additional C2 domains and two TM domains located in the middle of the protein for At1g03370 and At5g50170 (Table 3). The C2 domains might be involved in protein binding to membranes enriched in negatively-charged lipids, such as the PM. Few data are available concerning plant LAMs. VAD1-RFP fusion does not show a punctate pattern and seems to be localized in different cell compartments, including, PM, Golgi, tonoplast, ER, cytosol or nucleus when overexpressed (Khafif et al., 2017). This localization pattern might be linked to the RFP fused in C-terminal, close to the TM domain, which might alter membrane targeting of VAD1. VAD1 is a negative regulator of the programmed cell death hypersensitive response (HR) occurring in response to pathogen invasion to avoid their propagation in plant tissues (Khafif et al., 2017; Lorrain et al., 2004). Because of its role in cell death regulation, VAD1 is involved in pathogen resistance and the *vad1* mutant shows an enhanced resistance to pathogen attack linked to constitutive cell death activation (Khafif et al., 2017; Lorrain et al., 2004). Interestingly, the role of VAD1 in HR, as well as its nuclear localization, are dependent on the VASt, but not on the GRAM domain, suggesting that VAD1 localization and function might be regulated by lipid binding to the VASt domain (Khafif et al., 2017). The second LAM protein studied in *A. thaliana* is BAGP1, which also plays a role in biotic stress response by promoting basal immunity against the pathogenic fungus *Botrytis cinerea*. In response to pathogen infection, BAGP1 interacts with the protease APCB1 to promote the cleavage of BAG6 (Bcl2-associated athanogene), an autophagy activator inducing basal immunity against fungi (Li et al., 2016). However, the localization of BAGP1, how it regulates BAG6 cleavage and whether lipids are involved in the regulation of its function are still unknown. Overall, LAM proteins seem to play important roles in biotic stress response in plants, but despite their homology with yeast and mammalian LAMs, their localization and their ability to bind and/or transport lipids remain to be determined.

(Insert Table 3 here)

### 2.2.2 The Ups/PRELI family

Proteins of the Ups/PRELI family are soluble proteins located in the intermembrane space (IMS) of mitochondria acting in heterodimers with the molecular chaperone Mdm35/TRIAP1 to shuttle lipids from the outer (OM) to the inner (IM) membrane. Three Ups/PRELI and one Mdm35/TRIAP1 proteins exist in yeast (Ups1-3, Mdm35) and mammals (PRELID1, PRELID3a, PRELID3b, TRIAP1). The Ups1/PRELID1 and Ups2/PRELID3b proteins regulate mitochondrial CL and PE metabolism respectively by promoting the transport of lipid substrates, PA and PS respectively, from the OM to the IM where cardiolipin (CL) and phosphatidylethanolamine (PE) synthesizing enzymes are located (Aaltonen et al., 2016; Connerth et al., 2012; Miyata et al., 2016; Osman et al., 2009). Mdm35/TRIAP1 acts as a chaperone facilitating import and stability of Ups/PRELI proteins in the IMS (Potting et al., 2010, 2013). Mdm35/TRIAP1 dissociates from Ups/PRELI upon binding to membrane enriched in anionic lipids, such as CL, allowing lipid releasing and protein recycling (Aaltonen et al., 2016; Connerth et al., 2012; Watanabe et al., 2015). The Ups/PRELI proteins fold is characteristic of the StArkin domain superfamily with a seven-stranded  $\beta$ -sheet decorated with three flexible helices forming a hydrophobic cavity (Miliara et al., 2019; Watanabe et al., 2015). Interestingly, in plants, only one Ups/PRELI (At5g13070) and one Mdm35/TRIAP1 (At4g33100) homologs are found (Wideman & Muñoz-Gómez, 2016). At5g13070 protein is uncharacterized in *A. thaliana* but is predicted to be located in mitochondria IMS (Hooper et al., 2017; Schwacke et al., 2003). Sequence analysis suggests that At5g13070 is closer to the Ups2 than the Ups1 family, and might transport PS because of the absence of a conserved lysine residue (K58), present in Ups1 family, which impaired PS transport (Miliara et al., 2019; Wideman & Muñoz-Gómez, 2016). *In vitro*, yeast Ups2 can also transport PA, but *in vivo*, no decrease of CL is observed in  $\Delta ups2$  showing that Ups2 does not play an essential role in PA transport (Miyata et al., 2016; Osman et al., 2009). Thus, the plant Ups/PRELI protein might be involved in the transport of both PS and PA and/or alternative pathways might exist to transport PA for CL synthesis in the IM.

### 2.2.3 The StART family

StART domain-containing proteins are conserved throughout evolution (Ponting & Aravind, 1999). StART family is expanded in higher plants with 35 and 29 members in *A. thaliana* and in rice respectively whereas 15 members are found in humans and only one in yeast (Clark, 2020; Schrick et al., 2004). StART proteins are divided into subfamilies according to their domain organization and lipid binding specificity (Clark, 2020; Schrick et al., 2004). They are able to bind different ligands such as sterols, ceramides or phospholipids (Clark, 2020). As only members of the StARD2 subfamily have been shown to transport phospholipids (Kang et al., 2010), we will focus on this subfamily (for reviews about StART proteins, see (Clark, 2012, 2020)). In humans, there are three phospholipid-binding StART proteins (StARD2, StARD7 and StARD10) also called PC-TPs (PC transporter proteins), which are small proteins (around 200-300 aa) only composed of a StART domain (Clark, 2020; Schrick et al., 2004). StARD2 binds and transports PC between liposomes *in vitro* (Wirtz, 1991). It folds into a nine-stranded curved  $\beta$ -sheet with four helices forming a binding pocket accommodating one PC molecule (Roderick et al., 2002). This protein is localized in the cytosol and the nucleus and has been shown to regulate lipid droplet (LD) size in rat liver as well as the interplay between glucose and lipid metabolism (Clark, 2020; Kang et al., 2010; Kanno et al., 2007; Nicholls et al., 2017). In the nucleus, StARD2 also interacts with the Homeodomain (HD) transcription factor Pax3, involved in tissues and organs development (Buckingham & Relaix, 2007), and stimulates its activity (Kang et al., 2010; Kanno et al., 2007). Thus, it seems that StARD2 is more likely a PC-sensor regulating different cellular pathways than a PC transporter between membranes. In contrast, StARD7 is involved in PC transport from the mitochondrial OM to the IM in mammals (Horibata et al., 2016; Saita et al., 2018). *Stard7* KO or KD cell lines present a variety of mitochondrial defects including a reduced respiration rate and

ATP level, mtDNA damages and defects in mitochondrial cristae structure, highlighting the importance of this PC-transporter for mitochondria biogenesis and functions (Flores-Martín et al., 2016; Horibata et al., 2016; Saita et al., 2018; Yang et al., 2017). Two isoforms, StARD7-I, with a 75aa N-terminal mitochondrial targeting sequence, and StARD7-II, co-exist in cells and are able to bind PC and ceramides, but only PC is transported between liposomes (Bockelmann et al., 2018; Horibata & Sugimoto, 2010; Saita et al., 2018). StARD10 is able to bind and transport PC and PE *in vitro* and its transport activity is inhibited by phosphorylation, showing that lipid transfer and membrane binding can be regulated by post-translational modifications (Olayioye et al., 2005, 2007). In lung alveolar type II epithelial cells, StARD10 interacts with the ER lyso-PC acyltransferase 1 (LPCAT1) and promotes lipid transport on lamellar bodies (LB) where lipids are stored until secretion in the lung surfactant (Goss et al., 2013; Lin et al., 2015).

Six homologs of the PC-PT family can be found in *A. thaliana* (Table 4). They are longer than their yeast and human counterparts (around 400aa) and predicted to possess one or several TM domains (Schrack et al., 2004). TM domain-containing StART proteins are also found in rice and chickpea (Satheesh et al., 2016; Schrick et al., 2004). They are expressed at different stages of plant development and expression of some of them are induced or repressed in response to biotic or abiotic stress (Satheesh et al., 2016). Information about the function, localization and lipid binding properties of these proteins is scarce. 3D homology modeling of the At3g13062 shows that the StART domain overlaps with the crystal structure of StARD2 despite a low primary sequence similarity (Schrack et al., 2004). None of them is predicted to be targeted in mitochondria, questioning the existence of a StARD7 homolog in plants. Concerning the other StART domain-containing proteins, five members in *A. thaliana* have in C-terminal a domain of unknown function (DUF1336), which is plant-specific (Table 4) (Schrack et al., 2004). One member, EDR2, is a negative regulator of cell death during pathogen attack and binds to PI-4-monophosphate (PI(4)P) *via* its PH domain (Vorwerk et al., 2007), but the role of PI(4)P binding or of the StART domain has not been further investigated. It has to be noted that plants possess a unique subfamily of transcription factors composed of a StART domain associated to an homeodomain (HD) (21 members in *A. thaliana*, Table 4) (Schrack et al., 2004). In accordance with their putative role in the regulation of gene expression, they are predicted to be located in the nucleus and this localization was confirmed for some of them (Khosla et al., 2014; Lee et al., 2006; Schrick et al., 2014). Mutant analyses highlighted the importance of these transcription factors in plant development (Schrack et al., 2014). However, the role of the StART domains in the regulation of plant development, as well as their ligands, are still poorly understood. The StART domain of Glabra 2 (GL2), is required for the function of this transcription factor but not for its nuclear localization (Schrack et al., 2014). Interestingly, the StART domain of the mouse cholesterol transporter StAR can functionally replace GL2 StART domain and a mutation affecting StAR cholesterol binding site prevents functional complementation, indicating that sterol binding to GL2 is required for its transcriptional activator function (Schrack et al., 2014). In the same study, the authors analyzed the metabolites associated to the StART domain of three *A. thaliana* proteins (GL2, PDF2 and At3g13062) expressed and purified from yeast cells. Most of the detected metabolites are lipids. GL2 and PDF2 are associated to similar metabolites including lyso-PC, PC, DAG or sphingolipids whereas the putative PC-PT At3g13062 was associated to DAG and TAG (Schrack et al., 2014). However, because the study was performed in yeast, which contains only one sort of sterol (ergosterol) and missed some plant-specific lipids such as galactoglycerolipids, the lipid-binding ability of these *A. thaliana* StART domains might be misevaluated. Because of the association of a StARkin with a HD domain, regulation of gene expression by these plant-specific transcription factors might involve lipid binding.

(Insert Table 4 here)

### 2.3 ORP

ORPs (Oxysterol-binding protein (OSBP) related proteins), also called Osh (Oxysterol-binding protein homolog), are a widespread family of LTPs that regulate sterol and phospholipid homeostasis (Lipp et al., 2020; Moser von Filseck & Drin, 2016; Pietrangelo & Ridgway, 2018; Santos et al., 2020). Twelve and seven homologs are found in human and yeast genomes respectively and most of them are located at MCSs and are able to bind and transport sterols and PIPs between different organelles (Moser von Filseck & Drin, 2016; Pietrangelo & Ridgway, 2018; Schulz & Prinz, 2007). Some of them, Osh6/7 in yeast and their homologs in human ORP5/8, are also able to bind and transport PS and will be further described below (Lipp et al., 2020; Santos et al., 2020). ORP proteins all contain an ORD (oxysterol-binding related domain), which folds into a hydrophobic  $\beta$ -barrel accommodating one lipid molecule with a flexible N-terminal lid that regulates the opening/closing of the tunnel entry (Dong et al., 2020; Im et al., 2005; Maeda et al., 2013). The ORD domain can be associated to other domains regulating membrane binding and protein sub-cellular localization, such as a PH domain, a FFAT (Phenylalanine-Phenylalanine Acidic Track) motif targeting proteins to ER, or a TM domain (Pietrangelo & Ridgway, 2018; Schulz & Prinz, 2007). Interestingly, some of them (ORP5/8 and OSBP in human and Osh4/6/7 in yeast) use an original counter-exchange mechanism to transport lipids from one membrane to another against their concentration gradient (Chung et al., 2015; de Saint-Jean et al., 2011; Lipp et al., 2020; Moser von Filseck et al., 2015; Moser von Filseck & Drin, 2016). Osh6/7 and ORP5/8 are located at ER-PM MCSs where they play a role in PS transport to PM, PS being enriched in the cytosolic leaflet. Those proteins are able to bind PS or PI(4)P, which are abundant in the PM, by their ORD domain in a mutually exclusive manner (Maeda et al., 2013; Moser von Filseck et al., 2015). *In vivo*, Osh6/7 and ORP5/8 extract PS from its site of synthesis, the ER, to shuttle and release it into the PM where PI(4)P is extracted and shuttled back to the ER (Maeda et al., 2013; Moser von Filseck et al., 2015). The hydrolysis of PI(4)P by the ER phosphatase Sac1 is suspected to provide sufficient energy for PS transport and to maintain low PI(4)P content in the ER compared to PM, favoring directional PS transport (Lipp et al., 2020; Moser von Filseck & Drin, 2016). Interestingly, ORP5/8 are also located at ER-mitochondria and ER-LD MCSs. ORP5 interacts with LD *via* an amphipathic helix in the ORP domain and has been shown to regulate LD PS and PI(4)P content and LD size (Du et al., 2020). At ER-mitochondria MCSs, ORP5 and ORP8 interact with each other and with PTPIP51, an OM protein involved in mitochondria-ER tethering *via* its interaction with the ER protein VAP-B (Galmes et al., 2016; Stoica et al., 2014). ORP5/8 are involved in PS transport at ER-mitochondria to fulfill PE synthesis in the IM by PSD1 (Galmes et al., 2016; Rochin et al., 2020). Interestingly, most of the ORP5 proteins located at ER-mitochondria MCSs are close to cristae junctions (CJ), which are OM-IM MCSs maintained by the IM MICOS complex (Mukherjee et al., 2021; Rochin et al., 2020), suggesting that ORP5/8 might link PS transport from ER to the mitochondrial IM. As PIPs are barely detected in mitochondria, the transport of PS might be directed by a concentration gradient of PS rather than by a counter-exchange mechanism. In addition to its role in PS transport to mitochondria and PM, ORP5 is also involved in cholesterol transfer from low density lipoproteins (LDL) to late endosomes/lysosomes in Niemann Pick C (NPC) fibroblasts (Du et al., 2011) and regulates  $\text{Ca}^{2+}$  accumulation in the mitochondria and in the PM microdomains called caveolae (Pulli et al., 2018; Rochin et al., 2020). This example shows the versatility of functions and localizations associated to ORP proteins.

*A. thaliana* and rice genomes encode twelve and six ORP domain-containing proteins, respectively (Skirpan et al., 2006; Umate, 2011; Ye et al., 2020). *A. thaliana* proteins cluster in four groups and five proteins contain a PH domain and a FFAT motif that might be involved in their localization to ER and endomembrane compartments whereas the other members only have an ORD domain (Table 5) (Ye et al., 2020). Interestingly, when phylogeny analyses are performed with yeast

and mammalian proteins, no *A. thaliana* proteins group with the PS transfer proteins ORP5/8 and Osh6/7 (Skirpan et al., 2006; Ye et al., 2020), suggesting that ORP proteins might not transport PS in plants or that this transport is mediated by a more distantly related family of ORPs. All ORPs are expressed in different tissues and developmental stages, ORP3 group being the most highly expressed (Skirpan et al., 2006; Umate, 2011). Most of the ORPs genes are induced by biotic and/or abiotic stress as well as in response to toxic compounds such as metals (Umate, 2011). In accordance with this, GmOSBP is highly induced during high salt stress and senescence and its PH domain targets GFP protein to the nucleus in onion epidermal cells, suggesting the protein might be involved in gene expression regulation in soybean (Li et al., 2008). In petunia, PiORP1 is highly expressed in pollen tubes where it interacts with the receptor-like kinase PRK1, a protein essential for pollen tube development, leading to PiORP1 phosphorylation (Skirpan et al., 2006). PiORP1-GFP localizes in the cytosol and forms PH domain-dependent punctates in the PM, suggesting a localization at PM MCSs. However, the lipid binding specificity of PiORP1 and its role in pollen tube development, maybe to provide lipids to PM for elongation, is still unknown. In *A. thaliana*, ORP3A is localized in the ER *via* a WFDE motif required for its interaction with the ER VAP protein PVA12 (Saravanan et al., 2009). When this interaction is disrupted, ORP3A localizes to the Golgi compartment. *In vitro*, ORP3A ORD domain binds sitosterols but PVA12 interaction as well as the ER localization of ORP3A are independent of its ability to bind lipids (Saravanan et al., 2009). All these results suggest that ORP3A could shuttle sitosterol from ER to Golgi (Figure 3B). Plants ORP proteins could also be involved in the replication of some viruses that require specific lipids or membrane compartments for replication (Barajas et al., 2014; Nagy, 2015; Rodriguez-Peña et al., 2021). For instance, the bushy stunt virus (TBSV), a plant (+)RNA virus belonging to the Tombusvirus family, induces the formation of specific compartments arising from peroxisome membrane invagination, called spherules. Within spherules the assembly of the virus replicase complex (VRC) and the replication process occur, protected from degradation (Nagy et al., 2012; Rodriguez-Peña et al., 2021). The TBSV protein p33 is involved in the recruitment of the VRC to peroxisome membrane. Using a yeast model system to investigate the mechanism of TBSV replication, it has been shown that sterols are redistributed from the PM to the virus replication site and that sterols are essential for efficient replication of the virus (Barajas et al., 2014). Interestingly, p33 interacts with six *A. thaliana* ORPs (ORP3A-C and ORP4A-C) as well as with five VAP proteins and ORP3A and PVA12 have been shown to co-localize with p33 close to VRCs in *Nicotiana benthamiana* (Barajas et al., 2014). In both yeast and plant systems, the presence of a replicative TBSV virus induces ER-peroxisomes MCSs formation close to spherules, p33 being located in both peroxisomes and ER membranes (Barajas et al., 2014). This suggests that p33 induces peroxisome-ER MCSs formation and recruits ORP proteins to promote sterol transfer from ER to peroxisomes and to stimulate TBSV replication and spherule formation.

(Insert Table 5 here)

#### 2.4 VPS13-like protein family / Chorein\_N domain-containing proteins

VPS13-like proteins are highly conserved from yeast to human. This protein family is composed of two main protein types: the huge (>3000 aa) vacuolar protein sorting 13 (VPS13) and the autophagy-related 2 (ATG2) proteins. Among all the functional domains found in VPS13-like proteins, the N-terminal Chorein\_N domain and the adjacent VPS13\_N domain, both involved in lipid binding are the best conserved (De et al., 2017; Pfisterer et al., 2014). In VPS13 proteins, these domains are usually followed by a long region containing repeating coiled regions and the characteristic Vps13 adaptor binding (VAB) domain. Their C-terminus is typically composed of an APT1-homology domain, an ATG-homology domain (ATG\_C) and finally a C-terminal PH domain. Most of these domains are involved in the subcellular targeting of VPS13 proteins (Dziurdzik & Conibear, 2021). VPS13-like proteins associate to membranes and MCSs and are implicated in a large variety of cellular processes

like sporulation and *trans*-Golgi network homotypic fusion in yeast (De et al., 2017; Park & Neiman, 2012; Rabitsch et al., 2001) or regulation of autophagy, cytoskeletal architecture and cell survival in humans (Föller et al., 2012; Muñoz-Braceras et al., 2015). The *Saccharomyces cerevisiae* genome contains only one VPS13 protein, which localizes to nuclear-vacuolar junctions, mitochondria-endosome and vacuole-mitochondria MCSs depending on the cell physiological condition (Bean et al., 2018). Four homologs have been identified in human which also localize to different MCSs (for recent review, see (Dziurdzik & Conibear, 2021)). Yeast and human genomes encode one and two ATG2 protein respectively, that are localized to ER-autophagosome MCSs (Graef et al., 2013; Suzuki et al., 2013) and are part of the autophagosome forming machinery (Nakatogawa, 2020). Both VPS13 and ATG2 proteins play a major role in lipid transport. *In vitro*, the N-terminal parts of *Chaetomium thermophilum* VPS13 and human ATG2A are able to bind at least 10 glycerolipids and to transport them between liposomes, strongly suggesting they are non-specific glycerolipid transporters (Kumar et al., 2018; Valverde et al., 2019). Structural analyses show that the N-terminal extremity containing the Chorein\_N domain forms a scoop-like hydrophobic cavity that could presumably accommodate glycerolipids and that is extended by a long hydrophobic groove with a rod-like  $\beta$ -strand structure (Kumar et al., 2018; Li et al., 2020; Osawa et al., 2019; Valverde et al., 2019). Due to their localization at MCSs, their lipid-friendly elongated groove structure and their size exceeding 20 nm (De et al., 2017), it has been broadly hypothesized that VPS13 proteins form bridges between membranes at MCSs to mediate non-specific bulk glycerolipid transport by a bridge-like mechanism (Figure 2E) (Dziurdzik & Conibear, 2021; Kumar et al., 2018; Li et al., 2020; Reinisch & Prinz, 2021).

Nothing is known about VPS13-like plant homologs. In *A. thaliana*, five Chorein\_N domain-containing proteins have been identified, three of which have already been previously identified (Table 6) (Michaud et al., 2017; Velayos-Baeza et al., 2004). Three unknown proteins (At4g17140, At1g48090 and At5g24740) harbor the typical VPS13 protein conserved domains, especially the Chorein\_N domain and the VPS13\_N domain present at their N-terminal extremity. Given the high degree of homology found with other VPS13 proteins, we propose to rename At4g17140, At1g48090 and At5g24740 respectively AtVPS13A, AtVPS13B and AtVPS13C. Currently, nothing is known about AtVPS13A-C cellular localization. Predictions suggest a localization in the Golgi for all three proteins. Surprisingly, AtVPS13A and AtVPS13B have an additional VPS62-homology domain of unknown function in the middle of the protein. AtVPS13A has an additional predicted PH domain in the repeating coiled region and AtVPS13B harbors a C2 domain just before the VAB domain while AtVPS13C lacks the C-terminal PH domain (Table 6). The conservation of the domains involved in VPS13 protein targeting in yeast and mammals suggest that plant VPS13 proteins are also associated to multiple cell compartments, including MCSs. In addition, the presence of slight differences in domain organization and the presence of additional domains, like C2 or VPS62-like domains, preclude a higher complexity in the pattern of VPS13 protein localization and their regulation in plant cells. Interestingly, AtVPS13A/At4g17140 was identified in the mitochondrial OM proteome of *Arabidopsis thaliana* (Duncan et al., 2011). Even though the GFP fusions of the 200 N-terminal and C-terminal amino acid residues failed to give a consistent localization, this study gives a first hint for the potential mitochondrial localization of AtVPS13A. AtVPS13A was also found in the *A. thaliana* mitochondrial complexome and migrated at a molecular weight of 650 kDa on BN-PAGE (Senkler et al., 2017). An FFAT motif localized in the N-terminal region of AtVPS13A was also identified, suggesting an association with the ER membrane (Slee & Levine, 2019). In light of these preliminary results, AtVPS13A-C seem to be good candidates as novel VPS13-family LTPs in plants and require further investigation. At3g19190 corresponds to a plant ATG2, also known as PEUP1. Its domain organization and its cellular functions are similar to yeast and mammalian ATG2 proteins (Chen et al., 2021; Ding et al., 2018).

(Insert Table 6 here)

## 2.5 The Sec14-superfamily

The Sec14 domain is widely conserved in Eukaryotes and the Sec14-superfamily is expanded in higher Eukaryotes where more than 20 members can be found in mammals and plants whereas yeast contains only six Sec14 proteins (Bankaitis et al., 2010). In lower Eukaryotes, proteins of this family usually contain only one Sec14 domain whereas in higher Eukaryotes, the Sec14 domain is mainly associated to other domains including the GOLD (Golgi dynamics) domain, the PRELI domain or the plant-specific nodulin domain (Bankaitis et al., 2010). Because of their high number and huge diversity in domain organization, the Sec14 proteins are involved in a wide range of cellular processes including membrane trafficking, lipid metabolism and signaling pathways by regulating PIPs levels and the activity of different GTPases (Bankaitis et al., 2010). Sec14 domains fold in an approximately 280 aa globular structure with two lobes, formed by an assembly of  $\alpha$ -helices and one  $\beta$ -sheet (for a review, see (Bankaitis et al., 2010)). The lipid-binding pocket is composed of a  $\beta$ -sheet defining the pocket floor and of  $\alpha$ -helices forming the wall, the number of  $\beta$ -strands and the orientation and number of  $\alpha$ -helices varying among the Sec14 proteins. A helical flexible gate regulates the entry of the cavity with an “open” conformation in absence of lipids and a “closed” conformation when a lipid molecule is inserted in the binding pocket (Bankaitis et al., 2010). Sec14 proteins are able to bind and transport PI, as well as a second ligand that can be diverse hydrophobic compounds like PC, PS, PE, sterols, squalene or  $\alpha$ -tocopherol (Li et al., 2000; Schaaf et al., 2008; Tripathi et al., 2019). The role and mechanisms of action of Sec14 PIPTs have been mostly studied in yeast where they are involved in PIPs metabolism and signaling, vesicular trafficking, lipid droplet biogenesis or PS synthesis (Lipp et al., 2020; Ren et al., 2014; Schaaf et al., 2008). It appears that Sec14 proteins are likely involved in regulatory processes rather than in interorganellar bulk lipid transport. The most studied protein is yeast Sec14, that regulates PIPs metabolism and vesicular trafficking at the *trans*-Golgi network (TGN) (for reviews, see (Bankaitis et al., 2010; Grabon et al., 2015; Lipp et al., 2020). Sec14 binds and transports PC and PI in an ATP-independent manner and regulates PI(4)P level in the Golgi by transporting PI in this organelle and promoting its phosphorylation by the PI(4) kinase Pik1 (Bankaitis et al., 1990; Lipp et al., 2020). The delivery of PI to the Golgi is coupled to the exchange with one PC molecule (Schaaf et al., 2008). From structural analyses of PC- or PI-bound Sec14 and Sfh1, the closest Sec14 homolog in yeast, it was possible to establish PC- and PI-binding barcodes, corresponding to aa residues establishing specific interactions with PI or PC polar head (Lipp et al., 2020; Schaaf et al., 2008). The main role of Sec14 is not to transport PI *per se*, but to render PI accessible to Pik1 for phosphorylation which otherwise happens with very low efficiency when PI is buried in a lipid bilayer (Lipp et al., 2020; Schaaf et al., 2008). This mechanism is called the “presentation model” in the literature (Kf de Campos & Schaaf, 2017; Lipp et al., 2020). It has to be noticed that efficient PI presentation to Pik1 requires PC binding, explaining why PC transfer activity is required for regulation of PIPs signaling by Sec14 and why PC metabolism is coupled to this signaling pathway (Grabon et al., 2015; Kf de Campos & Schaaf, 2017; Schaaf et al., 2008). *A. thaliana* and rice genomes encode for 32 and 27 Sec14 domain-containing proteins respectively (Table 7) (Huang, Ghosh, & Bankaitis, 2016). They are classified into three different families depending on domain organization and sequence similarities.

(Insert Table 7 here)

### 2.5.1 The Sec14-nodulin family

Fourteen proteins (AtSfh1-14) in *A. thaliana* present a Sec14 domain fused to a nodulin domain only found in plants (Huang, Ghosh, & Bankaitis, 2016; Montag et al., 2020; Vincent et al., 2005). The Sec14-nodulin organization is found in angiosperms and some gymnosperms but is absent

from more primitive plants such as moss and fern (Huang, Ghosh, & Bankaitis, 2016; Huang et al., 2016; Montag et al., 2020). Most of these proteins are highly expressed in tissues where extensive polarized membrane growth is required, such as in pollens or roots (Ghosh et al., 2015; Vincent et al., 2005). It is predicted to adopt a  $\alpha$ -helical coiled-coil structure composed of three antiparallel  $\alpha$ -helices (Ghosh et al., 2015). 3D modeling of AtSfh1 Sec14 domain shows a similar fold as for the yeast Sec14 protein and highlights a conservation of the yeast PI- and PC-binding barcodes among the Sec14-nodulin proteins (Huang et al., 2016). The ability of AtSfh1 and other Sec14-nodulin proteins to transport both PI and PC was confirmed by complementation of the yeast *sec14* mutant combined with *in vitro* transfer assays (Böhme et al., 2004; Huang et al., 2016; Vincent et al., 2005). These results suggest that this family might also regulate PIPs signaling by stimulating PIPs kinase activity. The occurrence of this mechanism for plant Sec14-nodulin proteins was further supported by functional analysis of AtSfh1, a protein mainly expressed during and involved in root hair elongation (Böhme et al., 2004; Vincent et al., 2005). During root hair elongation, a huge polarized transport of vesicles to the root tip elongation zone is required and involves the maintenance of a concentration gradient of PI(4,5)P<sub>2</sub> in the PM along the elongating root hair. AtSfh1 associates specifically to PI(4,5)P<sub>2</sub> in PM *via* a polybasic stretch located at the C-terminal of the nodulin domain (Ghosh et al., 2015; Vincent et al., 2005). The binding of AtSfh1 to PM and its oligomerization *via* the nodulin domain were suggested to promote the formation of microdomains enriched in PI(4,5)P<sub>2</sub> and to maintain the PI(4,5)P<sub>2</sub> gradient (Ghosh et al., 2015; Huang, Ghosh, & Bankaitis, 2016). In addition, AtSfh1 might also regulate the level of PI(4,5)P<sub>2</sub> by stimulating PI(4) kinase activity and PI(4)P synthesis, which can be subsequently used as a substrate for PI(4,5)P<sub>2</sub> synthesis. Because the Sec14 domain of several Sec14-nodulin proteins are able to complement yeast phenotype and to transport both PI and PC, it is likely that the regulation of PIPs metabolism by the presentation model is a general mechanism of action of Sec14-nodulin proteins (Huang, et al., 2016; Kf de Campos & Schaaf, 2017).

### 2.5.2 The Patellin family

Patellins are characterized by the association of the Sec14 domain to a GOLD domain and are present in plants as well as in metazoans. In plants, Patellins are found in angiosperms and gymnosperms and *A. thaliana* genome encodes six Patellin genes (AtPATL1-6) (Table 7) (Peterman et al., 2006; Zhou et al., 2019). Patellins have a variable N-terminal extension differing in both length and aa composition (Peterman et al., 2004, 2006). They are expressed in many tissues during plant development, in particular in cells with high mitotic activity, and are responsive to biotic and abiotic stress (Hua-Ying et al., 2019; Peterman et al., 2004; Tejos et al., 2018). Patellins do not contain TM domains and are found to be cytosolic and associated to membranes, in particular to PM (Peterman et al., 2004; Suzuki et al., 2016; Tejos et al., 2018; Wu et al., 2017). In dividing cells, AtPATLs are also localized to the cell plate, suggesting a role during cytokinesis (Peterman et al., 2004; Tejos et al., 2018). The PI-binding barcode, but not the PC-binding barcode, is conserved among the *A. thaliana* Patellins, suggesting they can transport PI and probably other yet unidentified substrates other than PC (Huang, et al., 2016; Peterman et al., 2004). All Patellins studied until now are able to bind several PIPs *in vitro* (Montag et al., 2020; Peterman et al., 2004; Suzuki et al., 2016). However, the association of AtPATL2 and AtPATL3 with the PM is mediated by protein-protein interactions *via* the GOLD domain and not by PIPs binding (Suzuki et al., 2016; Wu et al., 2017). Information concerning the roles of Patellins during plant development and in response to stress is scarce. AtPATL1 is involved in cold and salt stress resistance (Chu et al., 2018; Zhou et al., 2018) whereas AtPATL3 and 6 are involved in plant resistance to Alfalfa mosaic virus (AMV) by interacting with the AMV movement protein, impairing viral particle targeting to PDs and cell-to-cell movement (Peiro et al., 2014). A role in membrane trafficking during cytokinesis, salt stress response, vacuole biogenesis and autophagy is



also suspected. AtPATLs are recruited to cell plate during cytokinesis, but their role in the formation or maturation of such structure is unknown (Peterman et al., 2004; Tejos et al., 2018). AtPATL1 is overexpressed in response to high salts and interacts with the PM Na<sup>+</sup> transporter SOS1, reducing Na<sup>+</sup> transport and likely promoting salt stress tolerance (Zhou et al., 2018). Finally, AtPATL1 and 2 interact with AMSH3, a deubiquitinase enzyme involved in vesicular trafficking, vacuole biogenesis and autophagosome degradation (Isono et al., 2010; Katsiarimpa et al., 2013). Because of their ability to bind a wide range of PIPs, roles in cell signaling rather than bulk lipid transport are suspected (Zhou et al., 2019). Unfortunately, the molecular mechanisms involved in the regulation of Patellin function and whether their putative lipid transfer activity is required to sustain this function is still unknown.

### 2.5.3 Stand-alone Sec14

*A. thaliana* contains twelve stand-alone Sec14 proteins that can be divided into five clades that might define different biochemical properties and biological functions (Table 7) (Huang, Ghosh, & Bankaitis, 2016). A few proteins of this huge family were characterized and they seem to play a role in chloroplast development as well as in biotic and abiotic stress response (Hertle et al., 2020; Kearns et al., 1998; Kiba et al., 2014). Most of these proteins in plants were first identified by their ability to complement the yeast *sec14* mutant. This includes AtPITP11 (Jouannic et al., 1998), soybean Ssh1 and Ssh2 (Kearns et al., 1998) and *N. benthamiana* NbSec14 (Kiba et al., 2012). AtPITP11 is mainly expressed in leaves and flowers and transport PI *in vitro* (Jouannic et al., 1998), but no further information about its subcellular localization and function are available. Soybean Ssh1 is mainly expressed in leaves and roots whereas Ssh2 shows the highest expression level in developing seeds (Kearns et al., 1998). Both proteins are membrane associated but only Ssh2 is able to transport PI, but not PC, *in vitro*, whereas Ssh1 was not able transport PI and PC in the tested condition, suggesting it has no lipid transport activity or transports other unidentified molecules (Kearns et al., 1998). Both proteins bind PI(4,5)P<sub>2</sub> and Ssh1 also associates to PI(3,5)P<sub>2</sub> *in vitro* whereas Ssh2 seems to associate to PS and PA (Kearns et al., 1998). In response to hyperosmotic stress, a rapid increase of Ssh1 phosphorylation mediated by the salt-induced SPK1 and SPK2 kinases was observed, decreasing Ssh1 affinity for membranes (Monks et al., 2001). As Ssh1 increases *in vitro* PI(3) kinase and PI(4) kinase activities, it was proposed that Ssh1 regulates PIPs signaling in response to osmotic stress in soybean *via* modulation of PI kinases activity (Monks et al., 2001). NbSec14, a stand-alone Sec14 protein able to transfer PI and PC *in vitro*, is involved in lipid signaling during plant immune response to the bacteria *Ralstonia solanacearum* (Kiba et al., 2012, 2014). NbSec14 is upregulated during infection and NbSec14 siRNA plants show a higher susceptibility to *R. solanacearum*. In these lines, no increase in PA and DAG levels, two key lipids involved in plant immune response signaling, was observed upon infection, in accordance with a decreased DAG kinase, phospholipase D and phospholipase C activities in total plant extracts (Kiba et al., 2014). More recently, the first identified chloroplastic Sec14 protein, AtPITP7 (also called CPSFL1), was shown to be involved in chloroplast development and photoautotrophic growth (Hertle et al., 2020). AtPITP7 accumulates in plastid stroma vesicles and is involved in vesicular trafficking required for thylakoid biogenesis. *In vitro*, AtPITP7 binds PA, SQDG and PIPs but is only able to extract and transfer PI(4)P between liposomes (Hertle et al., 2020). Thus, this protein might regulate lipid signaling between the inner envelope of plastids and thylakoids.

## 2.6 nsLTPs

The non-specific LTP (nsLTP) is a land plant-specific class of LTPs that can bind a wide variety of substrates *in vitro*. They are encoded by large gene families, with 79 and 77 members in *A. thaliana* and rice respectively (Salminen et al., 2016). NsLTPs are small basic proteins (7 to 10KDa) characterized by the presence of eight conserved Cys residues. They fold into a compact globular

structure composed of four  $\alpha$ -helices with a C-terminal unstructured tail (for detailed reviews, see (Carvalho & Gomes, 2007; Salminen et al., 2016)). NsLTPs possess an N-terminal peptide sequence that targets proteins to the secretory pathway, most of them being then secreted in the apoplast space. They are soluble but some of them can bind membranes and liposomes *in vitro* while others can be post-translationally associated to a glycosylphosphatidylinositol (GPI) anchor. NsLTPs are able to bind a wide variety of substrates, like phospholipids, galactoglycerolipids, free FAs, acyl-CoA, lysolipids or prostaglandin (Kader, 1996; Salminen et al., 2016). Proteins from this family are mainly involved in 1) cell wall synthesis, 2) pollen and seed development, 3) embryogenesis, 4) defense against pathogens, 5) long-distance signaling and 6) stress response (Carvalho & Gomes, 2007; Edqvist et al., 2018; Kader, 1996; Salminen et al., 2016). Most of nsLTPs are likely not involved in the intracellular transfer of lipids dedicated to membrane biogenesis. However, such a role might be supported by two nsLTPs, AsE246 and MtN5, in legumes during nodulation in response to nitrogen starvation and by one nsLTP, GhLTPG1, involved in cotton fiber elongation (Deng et al., 2016; Lei et al., 2014; Pii et al., 2009).

During nitrogen starvation, legume roots are able to establish symbiotic relationships with rhizobial bacteria or arbuscular mycorrhizal fungi that will provide nitrogen to the plant in exchange of carbon (Downie, 2014; Udvardi & Poole, 2013; Verma, 1996). This symbiotic process occurs in special structures formed in roots of infected plants called nodules where bacteria are enclosed in a special cell compartment, the symbiosome, in which they will divide and differentiate into nitrogen-fixing bacteroids. Symbiosome membrane lipids arise from the host plant cell and a tremendous amount of lipid synthesis and transfer is required for nodule formation (Harrison & Ivanov, 2017; Verma, 1996). Symbiosome membranes formation relies on Golgi-derived vesicle trafficking (Harrison & Ivanov, 2017). They are composed of phospholipids (PC, PE, PI and PG) and DGDG (Gaude et al., 2004; Lei et al., 2014), suggesting that chloroplast and likely non-vesicular lipid trafficking might be involved in the biogenesis of these membranes. In line with this, AsE246, a nsLTP specifically expressed during nodulation and located to the symbiosome membrane, is required for nodule formation and symbiosomes development in *Astragalus sinicus* infected by the rhizobacteria *Mesorhizobium huakuii* (Chou, 2006; Lei et al., 2014). AsE246 is able to bind different phospholipids and galactoglycerolipids (Lei et al., 2014). However, whether AsE246 promotes lipid transport from cell organelles to symbiosome membranes remains to be defined. Another *Medicago truncatula* nsLTP, MtN5, plays a role in the regulation of root nodulation during *Sinorhizobium meliloti* symbiosis (Pii et al., 2009, 2012, 2013). MtN5 is expressed early during nodule formation and is required for optimal bacterial infection and nodule invasion. *In vitro*, MtN5 binds to some lyso-PC species (Pii et al., 2009). Lipidomic analyses of roots overexpressing MtN5 highlighted a global increase in lipid content, in particular of DGDG, MGDG, PE and glucosyl-ceramide. This increase is concomitant with the modification of the expression of genes involved in lipid metabolism and lipid transport (Santi et al., 2017). These results suggest that MtN5 might regulate lipid synthesis and/or transport during nodulation. Another role in the regulation of nodulation by lipid signalization has been proposed as 1) MtN5 is able to bind lyso-PC *in vitro* (Pii et al., 2009), a lipid signal involved in arbuscular mycorrhizal symbiosis (Drissner et al., 2007), and 2) overexpression of MtN5 triggers deregulation of the expression of genes involved in the synthesis of lipid signaling molecules such as PIPs kinases, phospholipases C or Sec14-like proteins (Santi et al., 2017). All these data suggest that non-vesicular lipid transport could also be involved in membrane biogenesis during plant-microorganism symbiosis in response to nitrogen starvation. This might be particularly true for DGDG, as this plastidial lipid has never been shown to be transported *via* vesicular routes.

Cotton fiber synthesis starts from ovule epidermal cells and is divided in four steps: 1) fiber initiation, 2) cell elongation, 3) secondary wall deposition and 4) maturation (Kim & Triplett, 2001).

The cell elongation step requires a huge amount of lipids to sustain membrane synthesis in growing cells (Wanjie et al., 2005). The GPI-anchored nsLTP GhLTPG1 is highly expressed in elongating fibers and is able to specifically bind and transport PI-monophosphates (Deng et al., 2016). GhLTPG1 harbors a peptide signal and a GPI anchor, both required for its localization to the PM (Deng et al., 2016). Silencing of GhLTPG1 slightly reduces cotton fiber length and the expression of cotton-fiber elongation genes. A small decrease in polar lipids, in particular of PI, was also observed (Deng et al., 2016), suggesting that GhLTPG1 might be involved in lipid transport to sustain fiber elongation.

### 3 Lipid transport mediated by other proteins

#### 3.1 NDPK-D

Nucleoside diphosphate kinases (NDPKs) are a family of proteins conserved throughout evolution with a primary role in the exchange of  $\gamma$ -phosphate between nucleosides-tri-phosphate and nucleoside-di-phosphate (Boissan et al., 2018). They act as symmetrical homo-hexamers and are present in different cell compartments where they can play a role in many cellular processes (Boissan et al., 2018; Janin et al., 2000). Interestingly, one well studied homolog in mammals, NDPK-D, is located in mitochondria IMS and is known to bind membranes and transfer CL (Epand et al., 2007; Schlattner et al., 2013; Tokarska-Schlattner et al., 2008). NDPK-D membrane binding is mediated by a cationic motif R89-R90-K91 located at the surface of the hexamer, which associates with negatively charged lipids, in particular CL (Tokarska-Schlattner et al., 2008). The R90 residue, specific to the mitochondrial NDPK-D ortholog in humans, is essential for CL and membrane binding (Tokarska-Schlattner et al., 2008). As one CL binding site is present per monomer, NDPK-D hexamers are able to tether liposomes containing CL *in vitro* and OM-IM *in vivo* (Epand et al., 2007; Kagan et al., 2016; Tokarska-Schlattner et al., 2008). Membrane binding inhibits NDPK-D phosphotransferase activity and promotes CL transfer from IM to OM, inducing apoptosis and mitophagy and linking NDPK-D lipid transport function to CL signaling (Kagan et al., 2016; Schlattner et al., 2013, 2018).

Two NDPK-D homologs are found in *A. thaliana* (NDPK3a and NDPK3b), NDPK3b being expressed at a very low level (Table 8) (Hammargren et al., 2007). Both proteins have been detected in mitochondrial proteome (Heazlewood et al., 2004) and NDPK3a-GFP fusion was found to be located in mitochondria (Carrie et al., 2009) or in mitochondria and plastids (Hammargren et al., 2007; Luzarowski et al., 2017). Interestingly, NDPK3a was also found in proteomic analysis of the MTL complex, a mitochondrial complex involved in lipid transport (see below) (Michaud et al., 2016). However, Western blot analysis suggests that this protein probably co-migrates with the MTL complex on native gel rather than being a real MTL complex component. In addition, the R90 residue required for membrane binding of human NDPK-D is not conserved in *A. thaliana*, suggesting that NDPK3 could not bind membrane lipids (Figure 4). However, in pea, NDPK3 is strongly associated with the intermembrane space (IMS) leaflet of the IM and interacts with the ANT carrier (Knorpp et al., 2003), suggesting that membrane binding could be mediated by protein-protein interactions in plants (Figure 3C(i)). Further analyses are required to understand if NDPK3a is a component of the MTL complex and if it transports CL between mitochondrial OM and IM.

#### 3.2 Enzymes involved in lipid metabolism

In yeast and mammals, several enzymes involved in lipid synthesis are enriched at MCSs, in particular at ER-mitochondria MCSs and at ER-PM MCSs (Gaigg et al., 1995; Pichler et al., 2001; Vance, 1990). In plants, enzymes involved in lipid metabolism have also been detected in ER-PM and in ER-plastids MCSs (Andersson et al., 2007; Larsson et al., 2007). In addition, during Pi starvation, the phospholipase D PLD $\zeta$ 2 is enriched at vacuole-mitochondria and vacuole-chloroplasts MCSs, whereas an even distribution along the vacuole membrane is observed when *A. thaliana* plants are grown in

Pi-sufficient conditions (Yamaryo et al., 2008). An increasing number of evidences suggests that such localization is important to provide an efficient transport of lipids between membranes. This is the case for instance in yeast for the transport of PS at ER-mitochondria MCSs, where the localization of PS synthase at this junction increases the efficiency of PS transport to mitochondria (Kannan et al., 2017). Several hypotheses can explain why the localization of lipid-synthesizing enzymes at MCSs is important for non-vesicular lipid transfer: 1) local synthesis can create microdomains with special lipid composition facilitating lipid extrusion and transfer; 2) the local enrichment of a lipid at MCSs can favor its transport by energy-independent LTPs following its concentration gradient, 3) the modification of a lipid at MCSs can promote the formation of lipid species more competent for non-vesicular transport (*i.e.* less hydrophobic), and/or 4) the coupling between synthesis and transfer can be important to rapidly regulate organelle biogenesis during cell division or in response to stress. In addition, several examples have demonstrated that enzymes can also work *in trans* at MCSs, meaning that they can modify a lipid substrate located in the juxtaposed membrane. This is the case of the phosphatidylserine decarboxylase PSD1 in mitochondria IM that can decarboxylate OM PS to produce PE at OM-IM MCSs (Aaltonen et al., 2016). This mechanism is involved in the regulation of lipid composition at MCSs but is not involved in the lipid transport process *per se*.

### 3.2.1 PC remodeling at ER-plastids MCSs

Lyso-PC can be spontaneously transferred between membranes because of its low hydrophobicity. In plants, lyso-PC synthesis at ER-plastids MCSs might be one of the mechanisms involved in the transport of lipid precursors from ER to chloroplast to fulfill galactoglycerolipid synthesis *via* the Eukaryotic pathway. This idea was supported by pulse chase experiments and by the presence of several enzymes involved in the synthesis of lyso-PC from PC and in its reacylation at ER-chloroplasts MCSs or in chloroplasts OE (Figure 3D(i)) (Bessoule et al., 1995; Jessen et al., 2015; Mongrand et al., 2000; Tan et al., 2011). In *Brassica napus*, the lipase BnCLIP1 is located at ER-chloroplast MCSs, where it might be involved in lyso-lipid synthesis from ER phospholipids (Tan et al., 2011). Andersson *et al.* show that cytosolic lipases can generate lyso-PC molecules which are subsequently used for galactoglycerolipid synthesis (Andersson et al., 2004). In *A. thaliana*, the long-chain acyl-CoA synthetases LACS4 and LASC9 are localized in the ER and the chloroplast OE respectively and double *lacs4lacs9* mutants show a decrease in the content of galactoglycerolipids arising from the Eukaryotic pathway (Jessen et al., 2015). Thus, these LACSs have been proposed to play a role in the creation of a local pool of acyl-CoA at ER-chloroplasts MCSs that might be used by LPCAT to promote PC synthesis in the chloroplast envelope (Jessen et al., 2015). In addition, LPCAT activity has been detected in the chloroplast envelope of several plant species (Bessoule et al., 1995; Karki et al., 2019). However, the analyses of *lpcat1lpcat2* mutants in *A. thaliana*, the two main enzymes responsible for LPCAT activity, demonstrated that LPCAT activity, and likely lyso-PC transport, is not essential for chloroplastic lipid synthesis *via* the Eukaryotic pathway (Karki et al., 2019). Interestingly, pulse chase labelling experiments performed in this work support a model in which the LPCAT1/2 enzymes are involved in the incorporation of newly synthesized chloroplastic FAs into PC by lyso-PC acylation. PC is then translocated back to the ER where it can also be synthesized by the *de novo* pathway from glycerol-3-phosphate and acyl-CoA, leading to two distinct pools of PC in the ER (Karki et al., 2019). Thus, this current model suggests that LPCAT1/2 are more likely involved in chloroplast to ER PC transport than in the Eukaryotic pathway of galactoglycerolipid synthesis. Transport of PC *via* the lyso-PC intermediate could also occur at ER-PM MCSs in plants where LPCAT activity has been detected in pea (Larsson et al., 2007).

### 3.2.2 DGD1

MGDG synthesis starts by the addition of a galactose residue to a DAG backbone. Bulk MGDG synthesis takes place at the plastid IE and is catalysed by MGD1, while MGD2/3 operate at the plastid

OE in non-photosynthetic tissues or during specific stress conditions, typically Pi starvation (Awai et al., 2001; Kobayashi et al., 2009). DGDG synthesis requires the addition of another galactose residue moiety to MGDG, a reaction catalysed by DGD1 and DGD2 at the plastid OE (Figure 3D(ii)) (Kelly et al., 2003). Hence, DGDG synthesis requires the transport of MGDG from the IE to the OE. The N-terminal region of DGD1, NDGD1, has been shown to promote lipid transport between the plastid IE and OE (Kelly et al., 2016). NDGD1 is necessary for DGDG synthesis in the OE. Furthermore, NDGD1 binds PA and enables fusion of PA-containing liposomes *in vitro* (Kelly et al., 2016). Thus, it has been suggested that NDGD1 could facilitate lipid transport between both chloroplast membranes by triggering membrane-hemifusion (Kelly et al., 2016). Whether DGD1 acts as a tether or as a direct lipid transport protein remains to be determined.

### 3.3 Enzymes flipping lipids between membrane leaflets

Several recent studies suggest that enzymes involved in lipid translocation between membrane leaflets act as key players in non-vesicular lipid transport between membranes, notably by acting in concert with LTPs. Flippases can flip lipids against their concentration gradient in an ATP-dependent manner to create asymmetric membranes while scramblases can translocate lipids between the two leaflets following their concentration gradient in an ATP-independent manner, thus, equilibrating lipids between membrane leaflets (Maxfield & Menon, 2016). The putative roles of these proteins in non-vesicular lipid exchanges might be 1) to ensure the selectivity and directionality of transport, 2) to facilitate the loading of lipids by LTPs, and/or 3) to facilitate the insertion of the transported lipid in the acceptor membrane (Dziurdzik & Conibear, 2021; Reinisch & Prinz, 2021). A good example of this mechanism is found in Gram-negative bacteria: lipopolysaccharide (LPS) is synthesized on the cytosolic leaflet of the IM and is subsequently transported to the extracellular leaflet of the OM (Sperandeo et al., 2017). LPS is first flipped across the IM by the flippase MsbA, then extracted from the IM by the LptB2FGC ABC transporter complex, ensuring the directionality of the transport. LPS transport through the periplasm is facilitated by LptACDFG proteins that form a hollow rod-like structure composed of hydrophobic  $\beta$ -jellyrolls reminiscent of the VPS13 hydrophobic groove (Thélot et al., 2020). The insertion of LPS in the OM and its translocation to the outer leaflet is ensured by the LptDE translocon (Sperandeo et al., 2017). A similar mechanism was proposed for lipid transport at ER-autophagosomes MCSs in yeast where the LTP Atg2 associates with the autophagosome-located Atg9 scramblase and with the ER-located scramblases TMEM41B and VMP1 (Matoba et al., 2020; Noda, 2021; Orii et al., 2021). Other LTPs, such as the human VPS13A or the yeast Osh6 protein have also been shown to associate with lipid scramblases (D'Ambrosio et al., 2020; Park & Neiman, 2020), suggesting further that lipid-flipping enzymes could play an active role in non-vesicular lipid transfer in association with LTPs.

In plants, lipid scramblases are also conserved but their role in lipid transport has never been investigated. However, in *A. thaliana*, a P4-ATPase flippase, ALA10, has been shown to regulate plastid MGDG synthesis in leaves (Table 8, Figure 3D(iii)) (Botella et al., 2016). ALA10 is located in the ER where it can interact with the ALA-interacting subunits (ALIS) ALIS1 or ALIS5. This association regulates ALA10 subcellular localization: in the ER close to PM when ALA10 is co-expressed with ALIS1 or in the ER close to chloroplasts when co-expressed ALIS5 (Botella et al., 2016). More recently, ALA10 localization was also shown to be impacted by its level of ubiquitination by the E3-Ubiquitin ligase PUB11, showing the complexity of the mechanisms regulating P4-ATPase localization in cells (López-Marqués et al., 2021; Salvaing et al., 2020). Overexpression of ALA10 increases the ratio MGDG/PC in leaves and the 18:2 content in chloroplastic PC, suggesting it can stimulate MGDG synthesis and enrich 18:2-PC species in chloroplasts (Botella et al., 2016). ALA10 interacts with the ER FA desaturase FAD2, involved in 18:1 acyl chain desaturation to 18:2, but not with FAD3, involved in 18:2 acyl chain desaturation to 18:3 (Botella et al., 2016). Thus, it was proposed that ALA10, by

interacting with FAD2, translocates PC species enriched in 18:2 from the luminal to the cytosolic leaflet of the ER, promoting a local enrichment of this lipid and favouring its transport by an unknown mechanism to chloroplasts. To explain the higher MGDG/PC ratio in ALA10 overexpressing plants, the authors suggested that the translocated PC could be a substrate for phospholipases D to generate PA, a lipid known to activate MGD1 activity (Botella et al., 2016; Dubots et al., 2012). This example illustrates that lipid flipping across membrane leaflets can also be involved in inter-organellar lipid transfer in plants.

## 4 Lipid transport mediated by protein complexes

### 4.1 The TGD complex

An important molecular effector implicated in ER to chloroplast lipid transport is the TGD (Trigalactosyldiacylglycerol) complex composed of at least five subunits: TGD1-5 (Table 8, Figure 3D(iv)). Plants deficient in any of the TGD proteins show substantial trigalactosyldiacylglycerol (TGDG) accumulation (hence their name) (Xu et al., 2003), reduction in growth and photosynthetic capacity (Li et al., 2012; Xu et al., 2008), and compromised embryogenesis (Xu et al., 2005). Importantly, they show reduced amounts of C18 acyl chains in *sn*-2 position of chloroplast lipids, consistent with an Eukaryotic lipid import defect into chloroplasts (Xu et al., 2003; Xu et al., 2008).

TGD1, TGD2 and TGD3 form a non-canonical ABC transporter system at the chloroplast IE. It probably derives from a Gram-negative bacterial ABC import system that was present in cyanobacteria prior to endosymbiosis (Roston et al., 2012). Bacterial ABC importers are divided into two structural categories but show conserved features comprising 1) two TM domains composed of multiple transmembrane helices forming a permease to allow substrate passage, 2) two nucleotide binding domains specialized in ATP hydrolysis that provide energy for substrate transport and 3) a usually periplasmic substrate binding domain (SBD) that captures and delivers the substrate to the transporter subunits (Beis, 2015; Ford & Beis, 2019; Hollenstein et al., 2007; Wilkens, 2015). TGD1 structure prediction is reminiscent of a half-permease unit of a bacterial ABC importer harbouring six transmembrane helices and is therefore thought to be the permease subunit of the TGD1-3 complex (Xu et al., 2003; Xu et al., 2005). Consistent with its putative role, TGD1 is an integral membrane protein localized in the chloroplast IE (Xu et al., 2005). TGD2 is the SBD-containing subunit of the TGD1-3 complex. In contrast to bacterial SBD subunits, TGD2 is anchored to the chloroplast IE by a N-terminal TM domain while the C-terminal part of the protein is located in the intermembrane space and specifically binds PA (Awai et al., 2006; Lu & Benning, 2009; Roston et al., 2011). A mycobacterial cell entry (MCE) domain is juxtaposed to the TM domain (Awai et al., 2006). Interestingly, bacterial MCE proteins are known to assemble into hexamers forming an elongated hydrophobic channel ideal for lipid transport between the bacterial OM and IM (Ekiert et al., 2017). A 25 amino acid sequence partially overlapping the MCE domain is sufficient to mediate PA binding, but the complete TGD2 C-terminus still provides better binding affinity suggesting the existence of multiple binding determinants (Lu & Benning, 2009). TGD3 is a small ATPase that provides the energy for the TGD-mediated lipid transport (Lu et al., 2007). TGD3 is a stromal protein that is associated with the chloroplast IE, consistent with its bacterial ABC importer counterparts (Figure 3D(iv)) (Lu et al., 2007).

TGD1-3 form a highly stable complex of about 500 kDa presumably composed of two TGD1 permease subunits, two TGD3 ATPase subunits and between 8 and 12 TGD2 SBD subunits (Roston et al., 2011; Roston et al., 2012). The large number of TGD2 proteins is surprising as it diverges from the canonical bacterial ABC importer architecture that usually contain only one SBD subunit. Why the TGD1-3 complex contains multiple SBD subunits is still unclear. Since TGD2 binds its putative substrate, PA, in a cooperative manner (Lu & Benning, 2009), it has been suggested that an increased amount of SBDs

could help to sense and bind PA even at extremely low concentrations (Roston et al., 2012). Alternatively, it has been proposed that the assembly of multiple SBDs could concentrate PA, a non-bilayer forming lipid, and thus facilitate lipid extraction from the donor membrane (LaBrant et al., 2018). Consistent with the latter hypothesis, TGD2 has been found to disrupt membranes *in vitro* (Roston et al., 2011). Furthermore, the MCE domain contained in TGD2 suggests that its oligomerization might form a lipid transport channel like MlaD in the bacterial non-canonical ABC lipid transporter (Chi et al., 2020; Ekiert et al., 2017; Thong et al., 2016).

The TGD complex also harbours two additional proteins: TGD4 and TGD5. TGD4 is a  $\beta$ -barrel protein that forms homodimers in the chloroplast OE (Figure 3D(iv)) (Wang et al., 2012, 2013; Xu et al., 2008). TGD4 is distantly related to the lipid A transporter D (LptD) subunit that transports LPS from the bacterial IM to the bacterial OM (see above). Even though TGD4 was initially thought to be localized in the ER, further investigations indicate a localization in the chloroplast OE (Wang et al., 2012; Xu et al., 2008). Thus, it has been proposed that TGD4 could be present at ER-chloroplast MCSs, thus providing a direct lipid transport route from the ER to the chloroplast (Wang & Benning, 2012). TGD4 binds PA with two cytosol-facing N-terminal domains that are both necessary and sufficient for lipid import, supporting a lipid transport function within the TGD complex (Wang et al., 2012, 2013). Another  $\beta$ -barrel protein, AtLPTD1, homologous to LptD like TGD4, is present in the chloroplast OE (Figure 3D(iv)) (Hsueh et al., 2017). Mutants depleted in AtLPTD1 show phenotypic traits similar to *tgd* mutants, including TGDG accumulation (Hsueh et al., 2017; LaBrant et al., 2018). AtLPTD1 is expressed during plant adaptation to Pi starvation and is presumably implicated in DAG import into chloroplasts (Hsueh et al., 2017). It is presently not known if AtLPTD1 is part of the TGD complex. TGD5 is a small glycine-rich protein interacting with the TGD1-3 complex and TGD4, strongly suggesting that it bridges the TGD complex subunits located in both chloroplast envelope membranes (Fan et al., 2015). A recent study showed that *A. thaliana* TGD5 mutants have a strong increase in plastid stromules (Itoh et al., 2021). Since stromules are known to promote ER-chloroplast contact sites (Schattat et al., 2011), it is tempting to hypothesize that stromule formation is the response to a lipid import defect caused by the lack of TGD5 subunit.

The current picture of the TGD complex suggests that ER-synthesized lipids in the chloroplast are directly channeled through the chloroplast OE and IE by TGD4 and TGD1-3, respectively (Figure 3D(iv)). A big gap of knowledge still concerns the nature of the transported lipid (LaBrant et al., 2018; Michaud & Jouhet, 2019). Since TGD2 and TGD4 have been shown to bind PA (Awai et al., 2006; Wang et al., 2012), it is tempting to speculate that PA is the transported lipid. However, a mathematical model mimicking chloroplast lipid synthesis *via* the Eukaryotic pathway suggests the import of DAG rather than PA (Maréchal & Bastien, 2014). Thus, PA could have a regulatory function of TGD, as it is the case for MGD1 for instance (Dubots et al., 2012). Remaining unanswered questions concern the connection between the TGD complex and the ER and its putative involvement in precursors import from the ER to the OE.

## 4.2 The MTL complex

The MTL complex is a complex involved in mitochondrial lipid transport, notably in response to Pi starvation (Michaud, 2018; Michaud et al., 2016). The MTL complex is a huge lipid-containing entity with roughly 200 proteins and migrating at about 800 kDa on native gel (Michaud et al., 2016). Proteomic analysis revealed that the MTL complex contains mainly mitochondrial proteins and also several proteins located in non-mitochondrial compartments, such as the plastid OE, suggesting a possible location at mitochondrial MCSs. Interestingly, all the components of the translocase of the outer membrane (TOM) complex and AtMic60 are present in the MTL complex (Table 8, Figure

3C(ii)). AtMic60 is a confirmed functional homolog of yeast Mic60, a core component of the mitochondrial contact site cristae organizing system (MICOS) complex (Pfanner et al., 2014).

MICOS plays a central role in mitochondrial membrane architecture, dynamics of protein import, lipid homeostasis and lipid trafficking (Michaud et al., 2017; Mukherjee et al., 2021; Rampelt et al., 2017). In yeast and mammals, Mic60, a core component located in the IM, interacts with multiple partners in the mitochondrial OM, *i.e.* the TOM complex, SAM50, VDAC and DNAJC11, thus tightly tethering the mitochondrial OM and IM (Mukherjee et al., 2021). AtMic60 interacts with AtTom40 and a decrease in AtTom40 content was observed in the MTL complex of *atmic60* mutants, suggesting that AtMic60 also modulates OM-IM tethering (Michaud et al., 2016). Furthermore, the abundance of AtMic60-AtTom40 in the MTL complex increases in Pi deprived conditions, suggesting a role in lipid remodeling (Michaud et al., 2016). Lipid analysis of the MTL complex in *atmic60* KO lines revealed that DGDG accumulation in the MTL complex is compromised whereas PE accumulates during Pi starvation, suggesting that PE export and DGDG import are impaired (Figure 3C(ii)). A role in intra-mitochondrial lipid trafficking was further supported by mitochondrial lipid analyses showing a decreased DGDG and increased PE levels in *atmic60* compared to WT during Pi starvation (Michaud et al., 2016). AtMic60 also destabilizes liposomes *in vitro*, suggesting that it could promote lipid desorption from membranes prior to transport (Michaud et al., 2016). Even if AtMic60 and AtTom40 were identified as key players, the exact lipid transport mechanism exerted by the MTL complex as a whole, as well as the role of its partners, remains to be unravelled. Since the MTL complex also encloses several extra-mitochondrial proteins, notably chloroplast OE proteins of unknown function, it is tempting to speculate that the MTL complex might form a structure connecting mitochondrial membranes to other cell compartments such as chloroplasts, promoting direct lipid transport between both compartments (Michaud et al., 2016, 2017). Such a hypothetical structure is reminiscent of the ER-mitochondria organizing network (ERMIONE) that has been suggested to organize ER-mitochondria MCSs functions in yeast and mammals and to be involved in ER to IM lipid transport (Wideman & Muñoz-Gómez, 2016).

## 5 Conclusion and perspectives

The general mechanisms described in mammals and yeast for non-vesicular glycerolipid transport are conserved in plants. For instance, most of the LTP families present in yeast and mammals are also found in plants, even if only a few of them have been characterized in terms of subcellular localization, lipid transport specificities and cellular functions. Peculiarities have to be highlighted concerning non-vesicular lipid transport in plants:

- Plants cope with a wide variety of stresses where lipid signaling and membrane remodeling play a crucial role in the adaptation process (Hou et al., 2016; Liu et al., 2019; Michaud & Jouhet, 2019). Thus, specific lipid signaling and trafficking systems might have been developed during evolution to empower the plant response to these particular situations. In accordance with this, many LTP families are expanded in plants and most of them are highly responsive to biotic and abiotic stresses. In addition, most of the plant LTPs characterized until now have a confirmed role in plant stress susceptibility (Table 1). It also has to be noticed that many *A. thaliana* LTP genes are predicted to be transcribed into several mRNA isoforms in the TAIR database, increasing the putative number of lipid transporter that could co-exist in a cell.
- Plant have a chloroplast which biogenesis requires extensive exchanges of lipids with the ER. Thus, specific lipid transport machineries, such as the TGD complex, have evolved during evolution to ensure chloroplast membranes biogenesis and functions. However, the mechanisms involved in ER-plastid MCSs formation and in the transport of lipids between both organelles remain poorly characterized. In addition, chloroplast lipids can be major



contributors for the biogenesis of extra-plastidial membranes in stress conditions, such as Pi starvation where DGDG is exported to mitochondria, PM and vacuoles, or nitrogen starvation in legumes where symbiosome membrane formation requires DGDG. Beside the poorly understood mechanisms involved in those transports, the question of whether chloroplast glycerolipids could also be involved in extra-plastidial membrane synthesis in normal growth conditions remains open.

- Finally, the synthesis cell wall structures in plants, such as cutin, wax or sporopollenin, requires the secretion to the extracellular space of hydrophobic components. To ensure this function, a specific family of LTPs, the nsLTPs, appeared in plants during evolution. In this huge family, some of them are also able to bind glycerolipids and are involved in membrane biogenesis during stress, highlighting that plants have evolved specific pathways for non-vesicular lipid transport.

In summary, the understanding of the processes involved in non-vesicular lipid transfer in plants is in its infancy. Many studies still have to be performed to understand how this process occurs and how it is regulated in response to stress.

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## TABLES

Roles	Characterized LTP proteins in plants
Lipid transfer between membranes	Syt1, Syt3, At1g73200, ORP3A, AtSfh1, AtPITP11, Ssh2, NbSec14
Membrane tethering	Syt1, Syt 3, Syt5, Syt7, At1g73200
Signaling	AtSfh1, Ssh1, AtPIPT7, MtN5
Vesicular trafficking	Syt2, AtPATL1, AtPATL2, AtPITP7
Plant development	PIORP3, AtSfh1, GhLTPG1
Abiotic stress response	Syt1, Syt3, AtPATL1, Ssh1, AsE246, MtN5
Biotic stress response	Syt1, Syt5, Syt7, VAD1, BAGP1, ERD2, ORPs, AtPATL3, AtPATL6, NbSec14
Regulation of gene expression	Syt7, GL2, HD-StART, GmOSBP

Table 1: Roles of the different lipid transfer proteins (LTPs) characterized until now in plants. A detailed description of the role of these LTPs can be found in this chapter.

AGI	Name	Sub-	Localization	Domain organization	References
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		family			
At2g20990	SYT1/SYTA	E-Syt	ER/ER-PM MCSs	TM-SMP-C2-C2	(Perez-Sancho et al., 2015)
At1g20080	SYT2/SYTB		Golgi/PM	TM-SMP-C2-C2	(Wang et al., 2015; Zhang et al., 2011)
At5g04220	SYT3/SYTC		ER-PM MCSs	TM-SMP-C2-C2	(Ruiz-Lopez et al., 2020)
At5g11100	SYT4/SYTD		ER (prediction)	TM-SMP-C2-C2	
At1g05500	SYT5/SYTE		ER/ER-PM MCSs	TM-SMP-C2-C2	(Ishikawa et al., 2020; Lee et al., 2020)
At3g18370	SYT6/SYTF		ER (prediction)	TM-SMP-C2-C2-C2-CC	
At3g61050	Syt7/AtCLB1		ER/ER-PM MCSs/nucleus	TM-SMP-C2-CC	(Ishikawa et al., 2020)
At3g60950		Mitochondria (prediction)	SMP-C2-DNasel-like		
At3g61030		Mitochondria (prediction)	SMP-C2-DNasel-like		
At1g73200		ER-Golgi MCSs (yeast complementation)	TM-PH-SMP	(Liu et al., 2017)	
At1g17820		ER-Golgi MCSs (by homology to At1g73200)	TM-PH-SMP		
At1g50260	NTMC2T5.1	Plastids (prediction)	TM-SMP-TM-TM-C2-TM		
At3g19830	NTMC2T5.2	Plastids (prediction)	TM-SMP-TM-TM-C2-TM		

Table 2: Genes of the synaptotagmin-like mitochondrial-lipid binding protein (SMP) family present in the *A. thaliana* genome. Protein localization were determined experimentally or the consensus localizations from SUBA and ARAMEMNON websites (prediction) are indicated (Hooper et al., 2017; Schwacke et al., 2003). The domain organization found for each protein is also indicated. CC: coiled-coil domain, PH: pleckstrin homology domain, TM: transmembrane domain.

AGI	Name	Localization	Domain organization	References
At1g02120	VAD1	PM, ER, golgi, cytosol, tonoplast, nucleus	GRAM-VaST-TM-CC	(Khafif et al., 2017)
At1g03370		Cytosol (prediction)	C2-VaST-TM-TM-C2-GRAM-VaST	
At3g59660	BAGP1	PM (prediction)	TM-C2-GRAM-VaST	
At5g50170		Cytosol (prediction)	C2-VaST-TM-TM-C2-GRAM-VaST	

Table 3: Genes of the lipid transfer at membrane contact sites (LAM) family present in the *A. thaliana* genome. Protein localization were determined experimentally or the consensus localizations from SUBA and ARAMEMNON websites (prediction) are indicated (Hooper et al., 2017; Schwacke et al., 2003). The domain organization found for each protein is also indicated. CC: coiled-coil domain, GRAM: glucosyltransferases, Rab-like GTPase activators and myotubularins domain, TM: transmembrane domain, VaST: VAD1 analog of StAR-related lipid transfer domain.

AGI	Name	Localization	Domain organization	References
At1g05230		Nucleus (prediction)		
At1g17920		Nucleus (prediction)		
At1g34650		Nucleus (prediction)		
At1g73360	HDG11	Nucleus		(Khosla et al., 2014)
At1g79840	GL2	Nucleus		(Schrack et al., 2014)
At2g32370		Nucleus (prediction)		
At3g03260		Nucleus (prediction)		
At3g61150		Nucleus (prediction)		
At4g00730	ANL2, AHDP	Nucleus (prediction)	HD-ZLZ-StART	
At4g04890	PDF2	Nucleus (prediction)		
At4g17710		Nucleus (prediction)		
At4g21750	ATML1	Nucleus (prediction)		
At4g25530	FWA	Nucleus (prediction)		
At5g17320		Nucleus (prediction)		
At5g46880		Nucleus (prediction)		
At5g52170		Nucleus (prediction)		
At1g30490	PHV-ATHB9	Nucleus (prediction)	HD-ZIP-StART	
At1g52170		Nucleus (prediction)		

At2g34710	PHB, ATHB-14	Nucleus		(Lee et al., 2006)
At4g32880	ATHB-8	Nucleus		(Lee et al., 2006)
At5g60690	REV, IFL1	Nucleus		(Lee et al., 2006)
At2g28320		Cyto/nucleus (prediction)		
At3g54800		Cyto/Mito/soluble (prediction)	PH-StART-DUF1336	
At4g19040	EDR2	ER, PM, endosomes		(Vorwerk et al., 2007)
At5g45560		Mito (prediction)		
At5g35180		Cyto/plaste/nucleus (prediction)	StART-DUF1336	
At1g55960		PM (prediction)	TM-StART	
At1g64720		Vacuole (prediction)	TM-StART	
At3g13062	Putatives PC-PT	PM (prediction)	TM-StART	
At3g23080		PM (prediction)	TM-StART-TM	
At4g14500		PM (prediction)	TM-StART-TM	
At5g54170		PM (prediction)	TM-StART-TM	
At4g26920		PM (prediction)	TM-StART	
At5g07260		Cyto/Mito (prediction)	StART	
At5g49800		Nucleus/Chloroplast (prediction)	StART	

Table 4: Genes of the StAR related transfers (StART) family present in the *A. thaliana* genome. Protein localization were determined experimentally or the consensus localizations from SUBA and ARAMEMNON websites (prediction) are indicated (Hooper et al., 2017; Schwacke et al., 2003). The domain organization found for each protein is also indicated. HD: homeodomain, PH: pleckstrin homology domain, TM: transmembrane domain, ZIP: leucine zipper, ZLZ: leucine zipper-loop-zipper.

AGI	Name	Localization	Domain organization	References
At2g31020	ORP1A	Cyto/Chloro (prediction)	PH-ORD	
At2g31030	ORP1B	Cyto (prediction)	ORD	
At4g08180	ORP1C	Nucleus/Chloro (prediction)	PH-ORD	
At1g13170	ORP1D	Nucleus/Chloro (prediction)	PH-ORD	
At4g22540	ORP2A	Nucleus (prediction)	PH-ORD	
At4g12460	ORP2B	Nucleus (prediction)	PH-ORD	
At5g02100	ORP3A	ER	ORD	(Saravanan et al., 2009)
At3g09300	ORP3B	Cyto (prediction)	ORD	
At5g59420	ORP3C	Cyto (prediction)	ORD	
At4g25860	ORP4A	Cyto (prediction)	ORD	
At4g25850	ORP4B	Cyto (prediction)	ORD	
At5g57240	ORP4C	Cyto (prediction)	ORD	

Table 5: Genes of the OSBP related protein (ORP) family present in the *A. thaliana* genome. Protein localization were determined experimentally or the consensus localizations from SUBA and ARAMEMNON websites (prediction) are indicated (Hooper et al., 2017; Schwacke et al., 2003). The domain organization found for each protein is also indicated. ORD: oxysterol-binding related domain, PH: pleckstrin homology domain.

AGI	Name	Localization	Domain organization
At4g17140	AtVPS13A	Golgi (prediction)	Chorein - VPS13_N - RCR - PH - RCR - VPS62 - VAB - APT1 - ATG_C - PH
At1g48090	AtVPS13B	Golgi (prediction)	Chorein - VPS13_N - RCR - VPS62 - C2 - VAB - APT1 - ATG_C - PH
At5g24740	AtVPS13C, SHBY	Golgi (prediction)	Chorein - VPS13_N - RCR - RCR - VAB - APT1 - ATG_C
At3g19190	ATG2/PEUP1	Nucleus/Golgi (prediction)	Chorein - VPS13_N - ATG2_CAD - ATG_C
At3g20720		Mitochondria/ Cytosol (prediction)	Chorein - VPS13_N

Table 6: Genes of the VPS13-like/Chorein\_N family present in the *A. thaliana* genome. Protein localization corresponds to the consensus localizations from SUBA and ARAMEMNON websites (prediction) (Hooper et al., 2017; Schwacke et al., 2003). The domain organization found for each protein is also indicated. APT1: Aberrant pollen transmission 1, PH: pleckstrin homology domain, RCR: Repeated coiled region, VAB: Vps13 adaptor binding.

AGI	Name	Sub-family	Localization	Domain organization	References
At4g34580	AtSFH1/COW1		PM/cytosol	Sec14-nodulin	(Böhme et al., 2004; Vincent et al., 2005)
At4g39180	AtSFH2		Cytosol (Prediction)	Sec14	
At2g21540	AtSFH3		Cytosol (Prediction)	Sec14-nodulin	
At1g19650	AtSFH4		Cytosol (Prediction)	Sec14-nodulin	
At1g75370	AtSFH5		Cytosol (Prediction)	Sec14-nodulin	
At4g39170	AtSFH6		Cytosol (Prediction)	Sec14-nodulin	
At2g16380	AtSFH7	Sec14-nodulin	Cytosol (Prediction)	Sec14-nodulin	
At2g21520	AtSFH8		Cytosol (Prediction)	Sec14-nodulin	
At3g24840	AtSFH9		Cytosol (Prediction)	Sec14-nodulin	
At2g18180	AtSFH10		Cytosol (Prediction)	Sec14-nodulin	
At5g47510	AtSFH11		Cytosol (Prediction)	Sec14	
At4g36490	AtSFH12		PM (Prediction)	Sec14-nodulin	
At1g55690	AtSFH13		Nucleus (Prediction)	Sec14-nodulin	
At5g56160	AtSFH14		Cytosol (Prediction)	Sec14	
At1g72150	AtPATL1	Patellin	Cytosol/Cell plate/PM	Sec14-GOLD	(Peterman et al., 2006; Tejos et al., 2018; Wu et al., 2017)
At1g22530	AtPATL2		Cytosol/Cell plate/PM	Sec14-GOLD	(Suzuki et al., 2016; Tejos et al., 2018; Wu et al., 2017)



At1g72160	AtPATL3		Cell periphery/PM/cytosol/Cell plate	Sec14-GOLD	(Peiro et al., 2014; Tejos et al., 2018; Wu et al., 2017)
At1g30690	AtPATL4		Cytosol/Cell plate/PM	Sec14-GOLD	(Tejos et al., 2018; Wu et al., 2017)
At4g09160	AtPATL5		PM	Sec14-GOLD	(Tejos et al., 2018)
At3g51670	AtPATL6		Cell periphery/PM/cytosol/Cell plate	Sec14-GOLD	(Peiro et al., 2014; Tejos et al., 2018; Wu et al., 2017)
At4g08690	AtPITP1		Cytosol (Prediction)	Sec14	
At1g22180	AtPITP2		Cytosol (Prediction)	Sec14	
At4g36640	AtPITP3		Cytosol (Prediction)	Sec14	
At1g75170	AtPITP4		Cytosol (Prediction)	Sec14	
At1g05370	AtPITP5		Cytosol (Prediction)	Sec14	
At3g22410	AtPITP6	Stand-alone Sec14	Cytosol (Prediction)	Sec14	
At5g63060	AtPITP7/CPSFL1		Plastids	Sec14	(Hertle et al., 2020)
At1g01630	AtPITP8		Cytosol (Prediction)	Sec14	
At1g14820	AtPITP9		Cytosol (Prediction)	Sec14	
At3g46450	AtPITP10		Cytosol (Prediction)	Sec14	
At1g55840	AtPITP11		Cytosol (Prediction)	Sec14	
At5g47730	AtPITP12		Cytosol (Prediction)	Sec14	

Table 7: Genes of the Sec14 super-family present in the *A. thaliana* genome. Protein localization were determined experimentally or the consensus localizations from SUBA and ARAMEMNON websites (prediction) are indicated (Hooper et al., 2017; Schwacke et al., 2003). The domain organization found for each protein is also indicated. GOLD: Golgi dynamic.

AGI	Name	Localization	References
At4g11010	NDPK3a	Mitochondria/plastids	(Carrie et al., 2009; Hammargren et al., 2007; Luzarowski et al., 2017)
At4g23900	NDPK3b	Mitochondria (prediction)	
At3g25610	ALA10	PM, ER, ER-plastids MCSs, ER-PM MCSs	(Botella et al., 2016; Poulsen et al., 2015)
At1g19800	TGD1	Chloroplast inner envelope	(Xu et al., 2005)
At3g20320	TGD2	Chloroplast inner envelope	(Awai et al., 2006)
At1g65410	TGD3	Stroma	(Lu et al., 2007)
At3g06960	TGD4	Chloroplast outer envelope	(Wang et al., 2012)
At1g27695	TGD5	Chloroplast envelopes	(Fan et al., 2015)
At2g44640	atLPTD1	Chloroplast outer envelope	(Hsueh et al., 2017)
At4g39690	AtMic60	Mitochondrial inner membrane	(Michaud et al., 2016)
At1g22520	AtMic10	Mitochondria (Prediction)	
At3g20000	AtTom40	Mitochondrial outer membrane	(Duncan et al., 2011)

Table 8: Diverse genes playing a role in *A. thaliana* lipid transport. Protein localization were determined experimentally or the consensus localizations from SUBA and ARAMEMNON websites (prediction) are indicated (Hooper et al., 2017; Schwacke et al., 2003).

## LEGENDS TO FIGURES

**Figure 1:** Glycerolipid families found in plant cells. **A.** Glycerolipids are composed of a glycerol backbone esterified with two fatty acids (FA) in *sn-1* and *sn-2* positions. In *Arabidopsis thaliana*, the main FAs found in glycerolipids are 16 (C16) or 18 (C18) carbons-long and have up to three unsaturations (C16:0 to C16:3 and C18:0 to C18:3). In *A. thaliana*, the length of the carbon chain in *sn-2* position defines the origin of the glycerolipid backbone: a C16 is a signature of a backbone synthesized by the plastid by the Prokaryotic pathway while a C18 is a signature of a backbone synthesized in the endoplasmic reticulum by the Eukaryotic pathway. **B.** Three main glycerolipid families are found in plants depending on the nature of the polar head located in *sn-3* position of the glycerol backbone: 1) the phospholipids, all presenting a phosphate group in their polar head, 2) the galactoglycerolipids, having a polar head containing one or two galactose residues, and 3) the sulphoglycerolipid, with a sugar-based polar head containing a negatively charge sulfate group.

**Figure 2:** Mechanisms involved in non-vesicular glycerolipid transport at membrane contact sites. **A.** Spontaneous transfer of glycerolipids between membranes. **B-E.** Lipid transport mediated by lipid transfer proteins (LTPs). LTPs have a soluble domain with a hydrophobic cavity accommodating lipid molecule(s). They can be soluble (**B**), membrane bound (**C**) or anchored at two membranes (**D**), to shuttle lipids between membranes, or they can adopt a bridge-like structure forming a hydrophobic tunnel for lipid channeling between membranes (**E**). **F.** Lipid transport can be mediated by multi-subunits complexes crossing two or several membranes. **G.** Some membrane protein can promote non-vesicular lipid transport by favoring lipid extrusion or insertion from the donor or the acceptor membranes respectively. The different proteins and complexes using each mechanisms that will be discussed in this chapter are indicated.

**Figure 3:** Proteins involved in non-vesicular glycerolipid transport at different membrane contact sites (MCSs) in plant cells. **A.** Transport of diacylglycerol (DAG) by Syt1/3 at endoplasmic reticulum (ER)-plasma membrane (PM) MCSs. Syt1/3 are anchored to the ER by a transmembrane domain and to the PM by the binding of the C2 domains to phosphatidylinositides (PIPs). DAG transport is mediated by the synaptotagmin-like mitochondrial-lipid binding protein (SMP) domain. **B.** Putative transport of sitosterol by ORP3A at ER-golgi MCS. ORP3A interacts in the ER with the PVA12 VAP protein. **C.** (i) Putative transport of cardiolipin at mitochondrial (M) outer (OM)-inner (IM) membrane MCSs mediated by NDPK-3. NDPK-3 interacts in the IM with the ANT translocator. (ii) Digalactosyldiacylglycerol (DGDG) and phosphatidylethanolamine transport at OM-IM MCSs mediated by the mitochondrial transmembrane lipoprotein (MTL) complex during phosphate (Pi) starvation. In this complex, AtMic60 interacts with Tom40 and plays a key role in the lipid transport process. Because of the presence of chloroplast (C) proteins in the MTL complex, it could also be located at chloroplasts-mitochondria MCSs to mediate DGDG import during Pi starvation. **D.** Lipid transport at ER-chloroplast MCSs and outer (OE)-inner (IE) envelopes MCSs. (i) Putative lipid transport mediated by phosphatidylcholine (PC) remodeling at ER-chloroplasts MCSs. BnCLIP1 lipase could form lyso-PC from PC that could be acylated in the OE by lyso-PC acyltransferases (LPCAT) using a local pool of acyl-CoA generated by the long-chain acyl-CoA synthetases LACS4 and LACS9. (ii) The DGDG synthase DGD1 might play a role in OE-IE lipid transport thanks to its N-terminal extension. (iii) The ALA10 flippase could promote PC transport from the ER to the chloroplasts by promoting enrichment of 18:2-PC in the cytosolic leaflet of the ER. (iv) Import of lipids precursors in chloroplasts IE by the TGD complex and the LptD1 protein. TDG1, 2 and 3 form an ABC transporter in the IE

whereas TGD5 bridges the IE and OE via its interaction with TGD1/2/3 and TGD4. LptD1 is a homolog of TGD4 and might be involved in galactoglycerolipid synthesis during Pi starvation.

**Figure 4:** Sequence alignment of the mitochondrial NDPK enzymes from human (HsNDPK-D) and *Arabidopsis thaliana* (AtNDPK3a, b) showing the non-conservation in plants of the RRK motif involved in cardiolipin binding in humans.

**Figure 1**

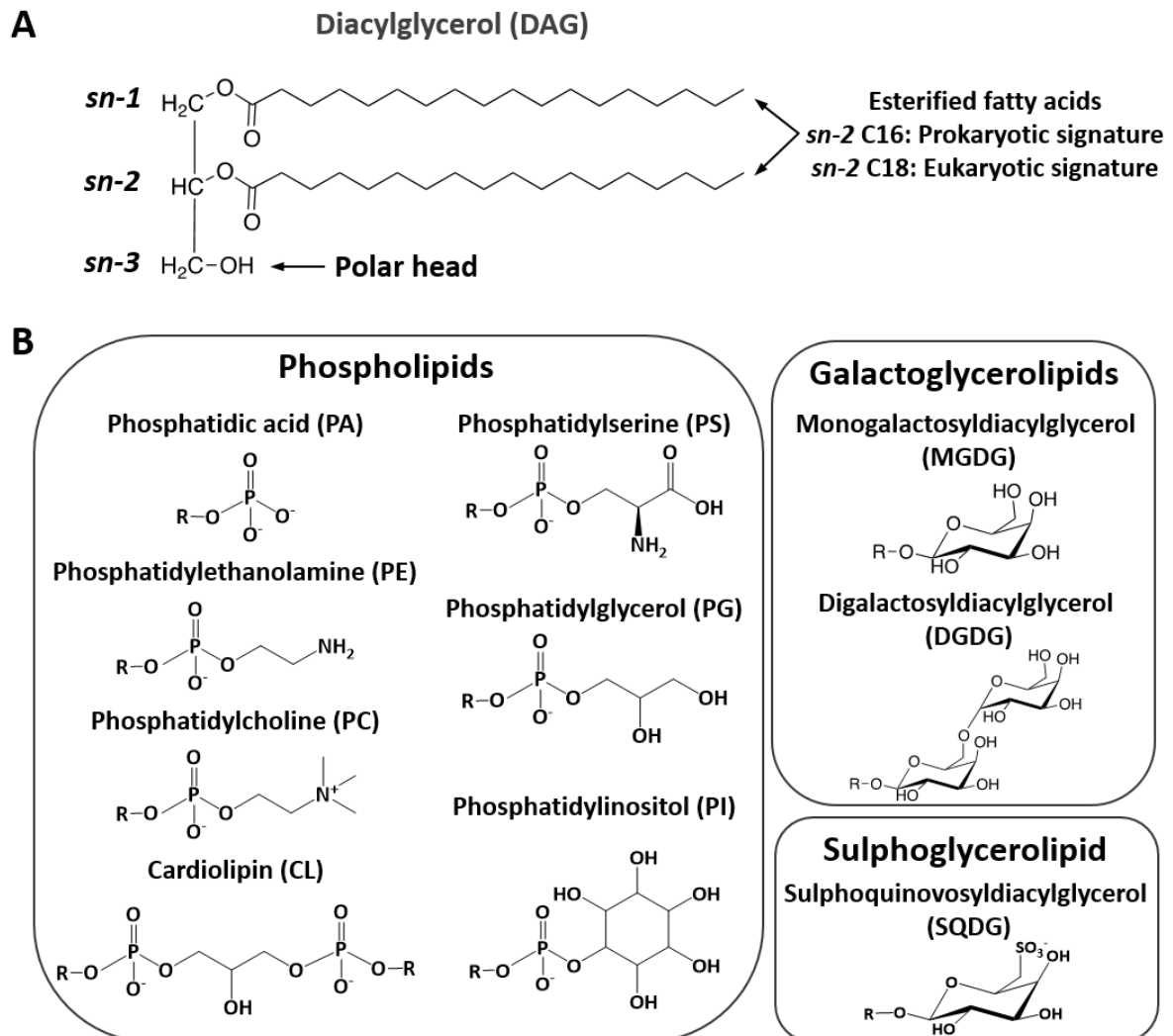


Figure 2

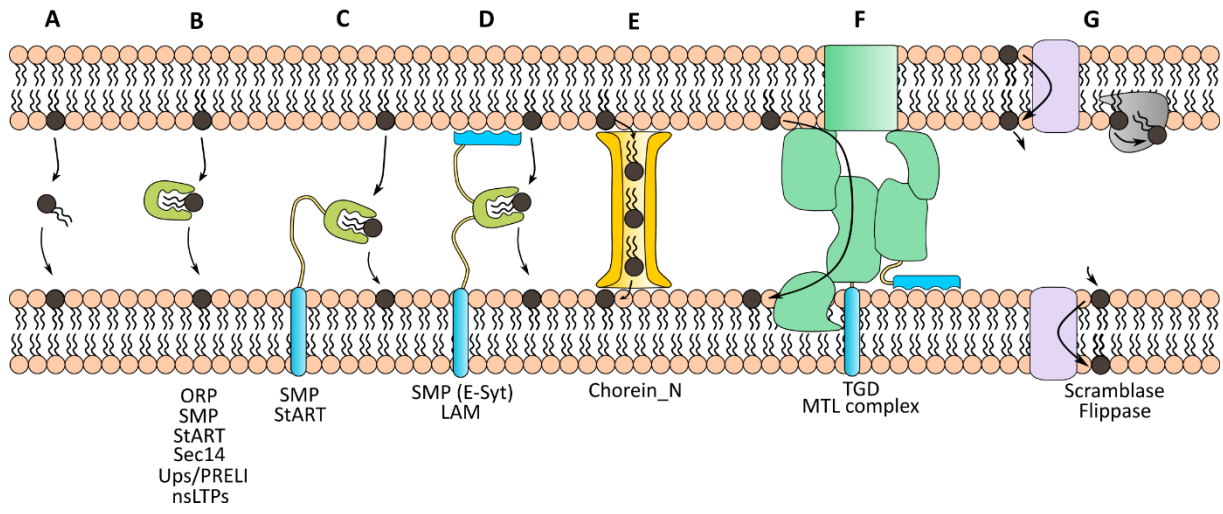
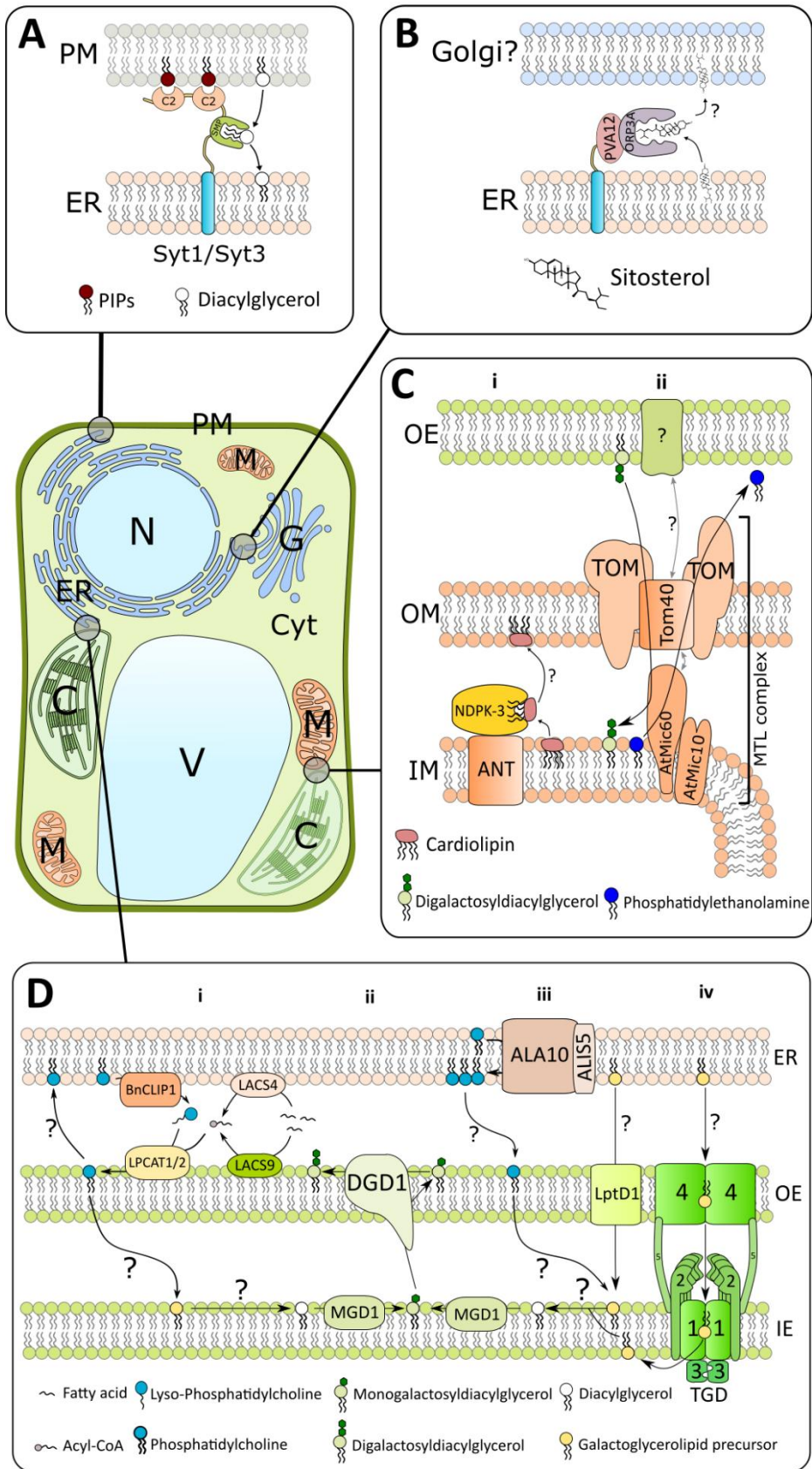


Figure 3



# Figure 4

HsNDPK-D	RRGFTLVGMKMLQAPESVLAEHYQDLRRKPFYPALIRYMSSGPVWAMWNEGYMWRASRA	122
AtNDPK3a	RKGFKLVGIKVIVPSKQFAQKHYHDLKERPPFNGLCDFLSSGPVIAMWNEGDGVIKYGRK	173
AtNDPK3b	RKGYKLVGIKVMVPSKQFAQKHYHDLKERPPFNGLCNFLSSGPVWAMWNEGEGVIKYGRK	172
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