

Supplemental Data

Supplemental text T1: Additional lipid binding domains

C1

These domains are zinc-finger domains consisting of ~50 amino acids. They preferably bind diacylglycerol (DAG) via the conserved sequence $\text{HX}_{12}\text{CX}_2\text{CX}_{13-14}\text{CX}_2\text{CX}_4\text{HX}_2\text{CX}_7\text{C}$. Some bind phospholipids. Atypical C1 domains have been shown to bind ceramide and enable protein-protein interactions (Colón-González and Kazanietz, 2006; Rahman and Das, 2015). Arabidopsis contains 137 C1-containing proteins.

FERM

The ~300-residues long FERM domain folds into three lobes (F1, F2 and F3), creating a basic cleft between lobes F1 and F3, where PI4P and PI(4,5)P₂ can bind (Hamada et al., 2000; Edwards and Keep, 2001; Carvalho et al., 2010). Between lobes F2 and F3, there is an acidic groove that facilitates protein-protein interaction (Hamada et al., 2000). In metazoans, FERM domains are especially found in proteins involved in the linking components of the cytoskeleton with the plasma membrane (Carvalho et al., 2010; Gough and Goult, 2018; Michie et al., 2019). Arabidopsis only contains one FERM protein (AT5G65930, KCBP/ZWICHEL), which like its mammalian homologues, is involved in microtubule and cytoskeleton organization (Buschmann et al., 2015; Tian et al., 2015; Chen et al., 2016; Liang et al., 2019). Its ability to bind PPIs remains to be shown.

PDZ

PDZ was initially characterized as a protein-protein interacting domain. However, approximately 30% of the mammalian PDZ domains are predicted to bind PPIs (Chen et al., 2012). In plants, the phospholipid binding properties of PDZ domains have not been analysed yet. Arabidopsis contains 16 PDZ proteins and there are indications that many more are present with less conserved PDZ domains (Gardiner et al., 2011).

Annexins

Annexins are Ca²⁺ dependent LBDs, consisting of a ~310 amino acid annexin core with four annexin repeats. Each repeat contains five α -helices that are connected via loops, resulting in a helix-loop-helix structure. The Ca²⁺ dependent membrane-binding sites are located on the loops, between the first and last two helices. Annexins bind anionic phospholipids, like PS, PI, and PA (Gerke et al., 2005; Clark et al., 2012; Yadav et al., 2018), although some annexins interact with PPIs independent of Ca²⁺, similar like C2 domains, e.g. human Annexin A2, which binds PI(4,5)P₂ (Rescher et al., 2004). Not all annexin repeats in a protein have the same phospholipid preference (Gerke et al., 2005; Clark et al., 2012; Yadav et al., 2018). Annexins have the ability to sense changes in [Ca²⁺] and are suggested to form Ca²⁺- or K⁺-permeable channels in lipid bilayers (Yadav et al., 2018). Arabidopsis has eight annexins, which are involved in membrane trafficking, cytoskeletal organization, cellular homeostasis, ion transport and have been implicated in various stress responses (reviewed in (Clark et al., 2012; Yadav et al., 2018).

Nlj16-like nodulin

A subgroup of SEC14 domain proteins contain a domain homologous to the *Lotus Japonicus* late nodulin Nlj16. Recently, Gosh et al. (2015) showed that these 'nodulin-domains' from SEC14 proteins contain the conserved motif, KKKKKKLLFFGF, localize to the plasma membrane and bind PI(4,5)P₂ with

high affinity, suggesting a novel LBD. In Arabidopsis and other plant species, including legumes, these Nlj16-like nodulin domains are only found in SEC14 domain-containing proteins.

GRAM

The GRAM (Glucosyltransferases, Rab-like GTPase Activators and Mytotubularins) domain consists of ~70 amino acids, which show a similar fold as the PH-domain (Begley et al., 2003) and is related to START (Sandhu *et al.*, 2018). It can bind PPIs but requires post-translational modifications and/or association with other proteins, as bacterial expressed-GRAM proteins require mammalian extract for binding (Choudhury et al., 2006). Recently, GRAM was shown to bind PA and PS (surprisingly, PPIs were not tested; Sandhu *et al.*, 2018). Arabidopsis contains 15 GRAM domain proteins, most being involved in abiotic stress responses, in particular related to ABA (Mauri et al., 2016). The latter includes GEM (GLABRA2 Expression Modulator), which is implicated in the spatial control of cell division, patterning and differentiation of root epidermal cells and root hair formation, and whose expression is highly responsive to ABA. GEM bound PI3P, PI4P, PI5P and PA, and interestingly, using immunoprecipitation was found to bind PIP5K9 *in vivo* (Mauri et al., 2016).

SYLF

SYLF (SH3YL1, Ysc84p/Lsb4p, Lsb3p, and plant FYVE protein) is a ~220 aa lipid-binding module that binds PPIs (Hasegawa et al., 2011). Arabidopsis has two SYLF proteins, At1g29800 and At3g43230 (CELL DEATH RELATED ENDOSOMAL FYVE/SYLF protein 1, CFS1), both containing also a FYVE domain. CFS1-SYLF binds PI3P, interacts with ENDOSOMAL SORTING COMPLEX REQUIRED FOR TRANSPORT 1 (ESCRT-1) and binds actin (Sutipatanasomboon et al., 2017).

Supplemental text T2: Interesting LBD-containing proteins

ARF-GAP domains (AGDs)

Arabidopsis has 4 AGDs (1-4) with a BAR domain, which also have a PH domain, an ARF-GAP domain and an ankyrin- (ANK-) repeat domain (Koizumi et al., 2005). With both a BAR and a PH domain, coincidence detection will likely play a role in lipid binding *in vivo*. Unfortunately, only for PH domain lipid binding preference was analysed, showing preference for PI5P and PI4P for AGD1 and AGD3, respectively (Koizumi et al., 2005; Yoo et al., 2012). Both BAR- and PH domain are essential for correct AGD subcellular localization (Naramoto et al., 2009). Furthermore, the BAR domain is also involved in the formation of AGD homodimers (Koizumi et al., 2005). Subcellular localization studies showed co-localization at ARA6-labelled endosomes, TGN/EE and PM for AGD1-3, while AGD4 was only at the PM (Naramoto et al., 2010, 2016). AGDs are ARF-GTPase-activating proteins (ARF-GAPs), which together with ARF-guanine nucleotide exchange factors (ARF-GEFs) regulate the activity of ARF GTPases. ARFs and their GEFs and GAPs play key roles in vesicle trafficking in mammalian and yeast. Evidence is accumulating that they perform a similar role in plants (Naramoto et al., 2010). AGD3 ARF-GAP activity is dependent on the presence of PI4P and to a lesser extent PI(4,5)P₂ (Naramoto et al., 2009).

Sorting nexins (SNXs)

There are three sorting nexins (SNXs) with a BAR domain in Arabidopsis, SNX1, SNX2a and SNX2b, all close homologues of human SNX1 and 2 (Vanoosthuysen et al., 2003). They also contain a PX domain that contributes to membrane binding. Like other BAR-containing proteins, plant SNX-BAR proteins require the BAR domain to form homo- or heterodimers (Pourcher et al., 2010). For SNX1 and SNX2b, lipid binding preferences of PX was determined to be PI3P and PI(3,5)P₂, and PI3P, respectively. (Phan et al., 2008; Hirano et al., 2015). The lipid binding of their BAR domain, however, was not analysed.

Like their mammalian homologues, plant SNX proteins require both PX and BAR domain for correct subcellular localization (Pourcher et al., 2010; van Weering et al., 2010) at the TGN and MVBs, in accordance to their PPI preference (Jaillais et al., 2006; Niemes et al., 2010; Pourcher, et al., 2010).

The SNX protein family is involved in protein trafficking, especially in response to environmental changes, such as temperature stress, nutrient availability as well as abiotic stress (Blum et al., 2014; Ivanov et al., 2014; Brumbarova and Ivanov, 2016; Heucken and Ivanov, 2018; Li et al., 2018). In mammalian and yeast, SNX-BAR proteins are required for a functional retromer complex formation, influencing membrane curvature and tubule formation as well as having a role in cargo sorting and in recognition of the destination compartment (van Weering et al., 2010). Plant SNX-BAR proteins are not required for a functional retromer complex (Pourcher, et al., 2010). Although, based on proteins that interact with SNX1 (Heucken and Ivanov, 2018), they are likely to have a role in cargo sorting and vesicle tethering. A role for the BAR domain in membrane curvature and tubule formation remains also to be addressed.

EREX and EREL

Endosomal Rab Effector with PX-domain (EREX) proteins are effectors of the canonical RAB5 proteins (Sakurai et al., 2016; Ren et al., 2020). EREX and EREL1 and 2 are cytosolic proteins that are only recruited to endosomal membranes when PI3P and active canonical RAB5 are present, where they are required for transport of storage proteins to PSVs. For the interaction with canonical RAB5s, the PX domain is essential (Sakurai et al., 2016). Detailed analysis of the rice homolog, GPA5, further showed its interaction with the vesicle tethering complexes CORVET and SNARE. Suggesting that recruitment of GPA5/EREX by active RAB5 to endosomal vesicles leads to the assembly of the vesicle tethering complexes, SNARE and CORVET, and docking of the vesicles with the PSV (Ren et al., 2020).

Membrane tethering through MCTP and SYT

Two large families of C2-containing proteins are the Synaptotagmins (SYTs) and Multiple C2 Domains and Trans-Membrane Region Proteins (MCTPs). Both are ER-PM tethers consisting of multiple C2 domains at one end and multiple transmembrane sites (TMS) on the other. While MCTPs have three to four C2 domains at their N-terminus and multiple TMS at the C-terminus (Brault et al., 2019), in SYTs this is reversed with the TMSs at the N-terminus and one to three C2 domains at the C-terminus. The latter also has a synaptogamin-like mitochondrial lipid-binding (SMP) domain in between the TMS and C2 domains (Ishikawa et al., 2020). Both MCTPs and SYTs use the TMS to anchor the ER and C2 domains to bind the PM. Each of the multiple C2 domains has their own specific binding conditions, e.g. Ca^{2+} and phospholipid requirement, to bind the PM (Jiménez et al., 2003; Brault et al., 2019) (Jiménez et al., 2003; Brault et al., 2019). Hence, it is suggested that the amount of Ca^{2+} present, influences the tightness of the PM binding, as such regulates the distance between ER and PM. Both SYTs and MCTPs were shown to locate at plasmodesmata and to regulate the thickness of the ER-desmotubule in and near the plasmodesmata, and as such, regulating/maintaining the gaps between desmotubules and PM (Brault et al., 2019; Ishikawa et al., 2020). Of the SYTs, it is known they do this by forming homo- or heterodimers. For an update on MCSs, check Bayer & Rosado (2020) in this Focus Issue.

SYTs also interact with proteins via their SMP domain. As such, SYT1 interacts with reticulon proteins, RTNLB3 and RTNLB6, and through this interaction likely helps to maintain ER-desmotubule morphology (Pérez-Sancho et al., 2015, 2016; Ishikawa et al., 2020). SYT1 also interacts with proteins of the SNARE complex, i.e. stigmasterol-binding protein ROSY1 (Pérez-Sancho et al., 2016). While no direct protein interaction has been identified for MCTPs, they may interact with proteins via the C2 domain closest to the TMS (Brault et al., 2019).

Currently, 16 MCTPs have been identified, forming a distinct clade in the C2 domain-phylogenetic tree (Suppl. Fig. S4). The synaptotagmin family, of which the SYTs are part of, is less obviously defined. SYT1-5 and SYT7 form a core clade, including two close homologs of SYT7 previously identified (Ishikawa et al., 2020), but show a different domain organisation: AT3G60950 has its TMS at its C-terminal, while AT3G61030 is missing both TMS and SMP domain. The core SYT clade also contains a close homolog to SYT1, which is missing TMS and SMP as well. SYT6 contains and SMP domain but shows to be phylogenetically distinct from the other SYTs (Ishikawa et al. 2020). Four SYT-like proteins (NTMC2T5.1/2 and NTMC2T6.1/2) are grouped in separate clades, close to SYT, indicating that the synaptotagmin family of transmembrane tethers is likely more extensive than what the core clade suggests.

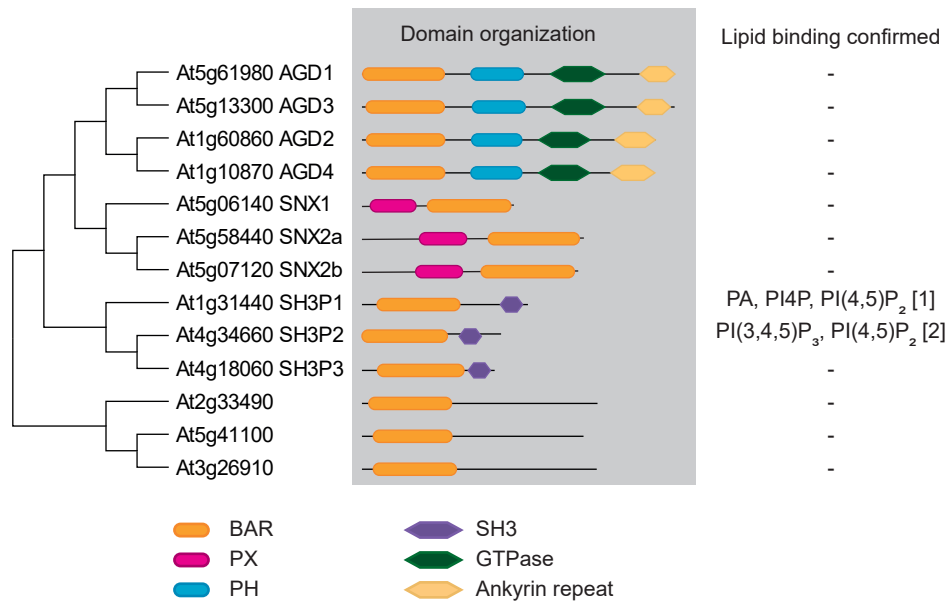
PLC

Another large clade of C2 domain-containing proteins belongs to the PI-specific phospholipase C (PLC) family. PLC cleaves off the entire headgroup of PI4P and PI(4,5)P₂, resulting in DAG and IP₂ or IP₃ (Munnik, 2014). Plant PLCs are involved in development and in abiotic- and biotic stress responses (D'Ambrosio et al., 2017; Di Fino et al., 2017; Li et al., 2017; van Wijk et al., 2018; Zhang et al., 2018a,b).

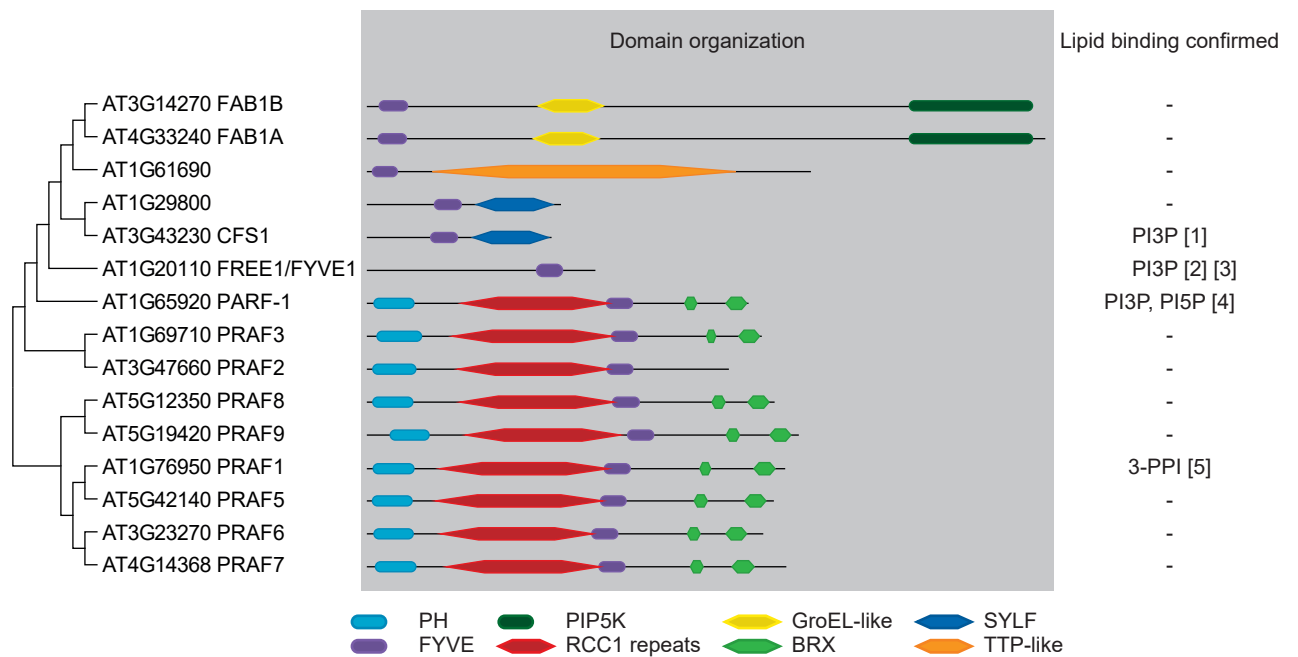
The core of eukaryotic PLCs consists of an EF-hand domain, an X/Y catalytic domain, and a C2 domain. While most mammalian PLCs have additional conserved domains for regulation, either at the N- or C-terminus of this core, including a PI(4,5)P₂ binding-PH domain, plant PLCs typically lack this, and it still remains unknown how they are regulated (Munnik, 2014). A crystal structure has been determined for rat PLCδ1 (Essen et al., 1996), and subsequent modelling approaches of PLC-C2 domains included plant PLCs, and showed their importance for PLC activity (Jiménez et al., 2003). This showed that the C2 domain inserts between the EF-hand and the catalytic domain, forming a rigid structure with the catalytic domain, such that its active site is properly presented to the membrane (Essen et al., 1996). The interaction is relatively weak though, and proposed to be held together by the strong interaction between C2 and the EF-hand domain (Jiménez et al., 2003). Absence of the C2 domain results in loss of catalytic activity (Jiménez et al., 2003), absence of the EF-hand domain also, but not affects its membrane localisation (Otterhag et al., 2001).

The binding of the PLC-C2 domain to membranes is Ca²⁺ dependent, and in metazoans preferably binds PS (Ananthanarayanan et al., 2002). For plants this is still unknown. Plant PLC-C2s have in addition to their conserved cation-coordinating amino acids at the CBR, also aromatic residues, which are proposed to insert into the membrane, enhancing their binding (Jiménez et al., 2003). Since plant PLCs lack additionally regulatory domains, their main regulation is likely to be dependent on Ca²⁺.

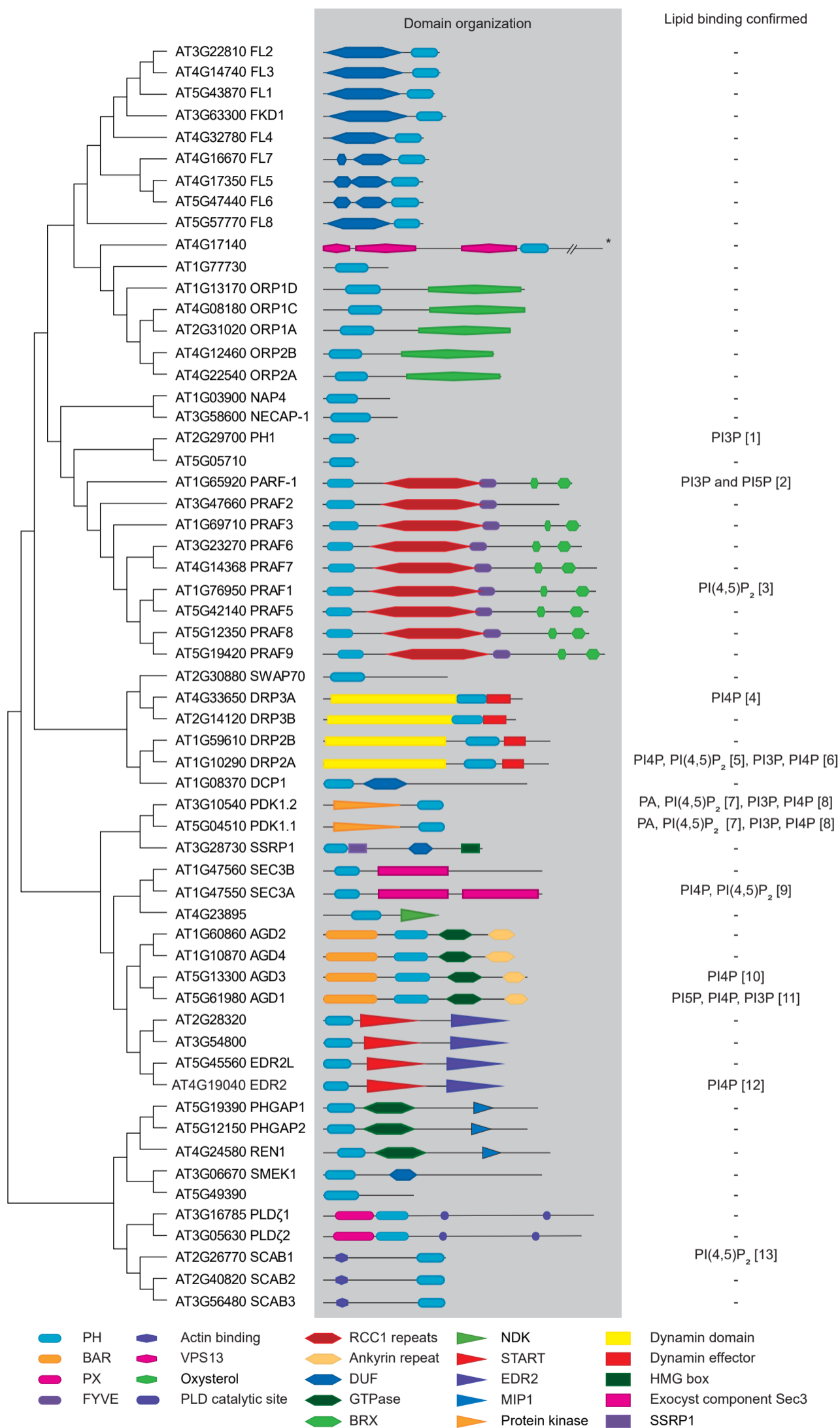
Supplemental Figures



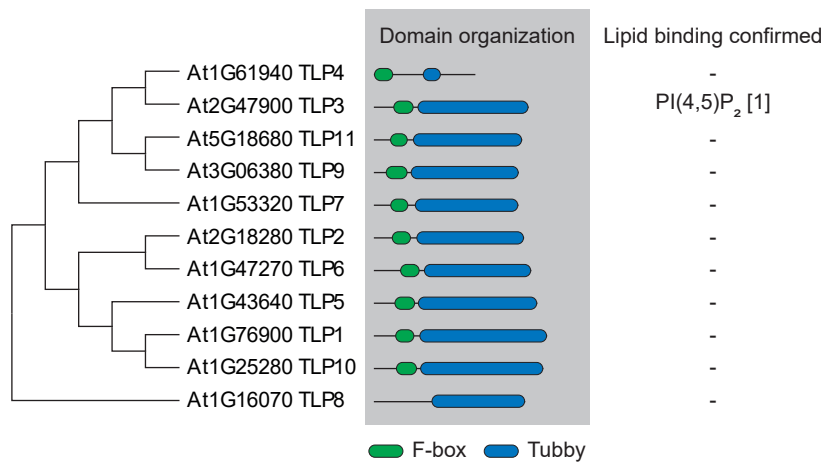
Supplemental Figure S1. Arabidopsis BAR proteins. Phylogenetic representation, schematic overview of additional domains (InterPro), and lipid binding of BAR. References: [1] Lam et al., 2001; [2] Ahn et al., 2017. Phylogenetic analysis was performed using MEGA X (Kumar, et al., 2018).



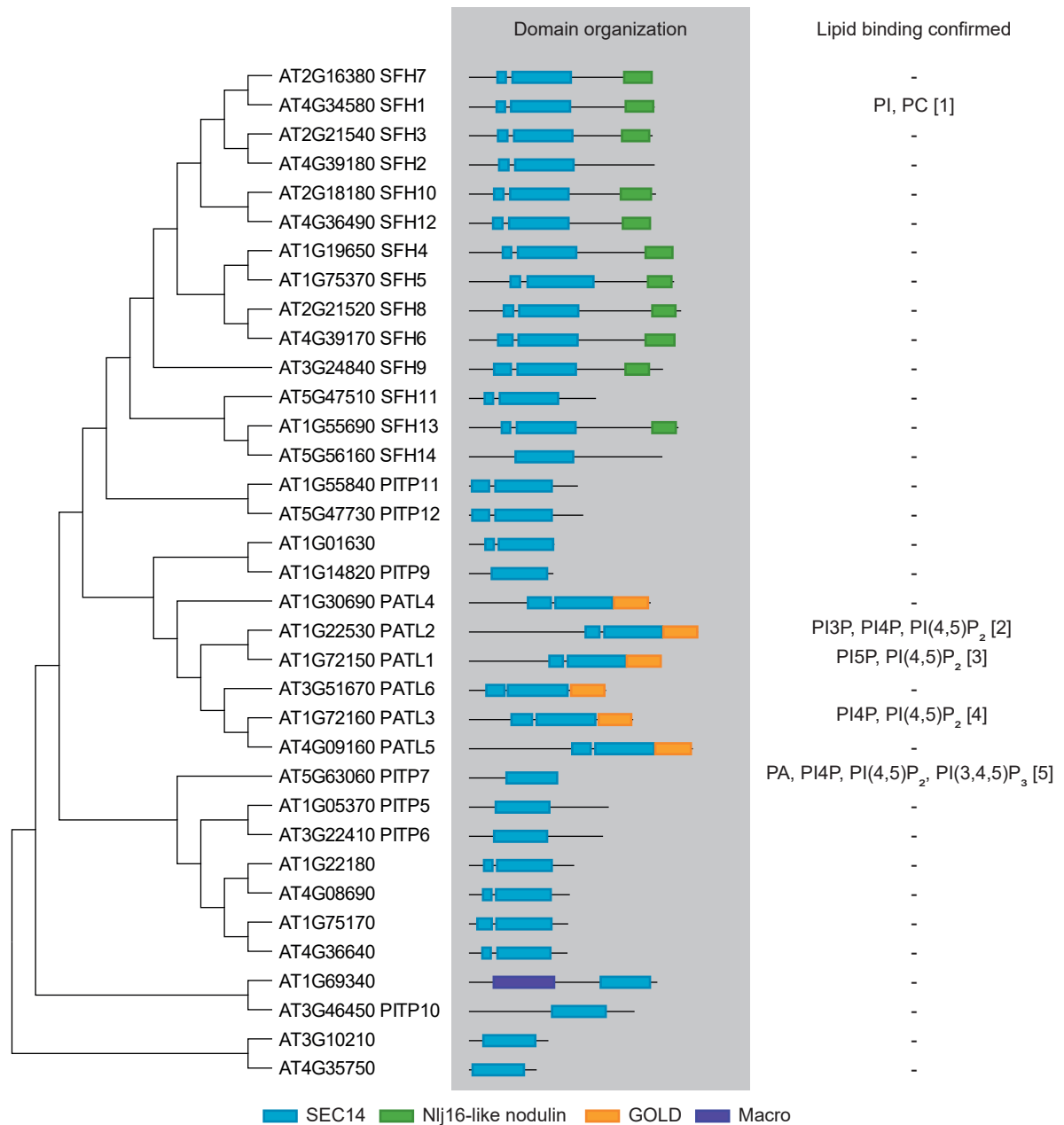
Supplemental Figure S2. Phylogenetic representation of Arabidopsis FYVE proteins with additional InterPro domains and lipid binding. References: [1] Sutipatanasomboon et al., 2017; [2] Gao et al., 2014; [3] Barberon et al., 2014; [4] Hetas and Drobak, 2002; [5] Jensen et al., 2001. Phylogenetic analysis was performed with MEGA X (Kumar, et al., 2018).



Supplemental Figure S3. Arabidopsis PH proteins. Phylogenetic representation, schematic overview of all domains found through InterPro and lipid binding. (*) At4G17140 is a protein of 4219 amino acids (approximately 4 times the size of PLDzeta1) with no domains in the C-terminal part of the protein. Lipid binding references: [1] Agorio et al., 2017; Dowler et al., 2000; [2] Heras and Drøbak, 2002; [3] Jensen et al., 2001; [4] Kim et al., 2001; [5] Lam et al., 2001; [6] Lee et al., 2002; [7] Anthony et al., 2004; [8] Tan et al., 2020; [9] Bloch et al., 2016; [10] Koizumi et al., 2005; [11] Yoo et al., 2012; [12] Vorwerk et al., 2007; [13] Zhang et al., 2012. Phylogenetic analysis was performed via MEGA X (Kumar, et al., 2018).



Supplemental Figure S5. Arabidopsis Tubby proteins. Phylogenetic representation, schematic overview of additional domains (InterPro), and lipid binding [1] Bao et al., 2014. Phylogenetic analysis was performed with MEGA X (Kumar, et al., 2018).



Supplemental Figure S6. Phylogenetic representation of Arabidopsis SEC14 proteins. A schematic overview of all domains found through InterPro. Phospholipid-binding preference of the SEC14 domain: [1] Huang et al., 2016, [2] Suzuki et al., 2016, [3] Peterman et al., 2004, [4] Wu et al., 2017, [5] Hertle et al., 2020. Phylogenetic analysis was performed using MEGA X (Kumar, et al., 2018).

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