SH Domain Proteins in Plants: Roles in Signaling Transduction and Membrane Trafficking

Xiaohong Zhuang and Liwen Jiang

Abstract The molecular mechanisms of signaling network molecules and dynamics are important topics in cell biology research. SH2 and SH3 are small scaffold molecules functioning in protein-protein interactions to mediate signal transduction pathways that are activated by protein kinases. In plants, several studies have uncovered the novel functions of SH2 or SH2-like domain containing proteins that are similar to the signal transducers and activators of the transcription (STAT) family. The *Arabidopsis thaliana* genome also contains SH3 domain-containing proteins (SH3Ps), but little is known about their functional roles in plant development and growth. In this chapter, we will summarize and discuss the evolutionary conservations of the plant SH2 and SH3 domain proteins with particular emphasis on their roles in regulating signaling transduction and membrane trafficking in plant cells.

Keywords SH2 domain · SH3 domain · Signaling transduction · Protein trafficking · BAR domain · Autophagy

1 Introduction

Plants and animals share the same habitat, but react to environmental cues differently. It is thus reasonable to expect that unique molecules and processes would be involved to mediate plant cell signal transduction. Key features of signaling

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processes in plant, like receptor dimerization, phosphorylation, kinase activation, also appear similar to those in animals, indicating that the mechanisms of receptor-mediated signaling are conserved within eukaryotic kingdoms (von Zastrow and Sorkin 2007). In plants, leucine-rich repeat receptor-like protein kinases (LRR RLKs) represent the largest plasma membrane-localized subfamily of receptors in Arabidopsis and function in diverse signaling pathways for plant development and pathogen defense (Shiu and Bleecker 2001; Antolin-Llovera et al. 2012; De Smet et al. 2009). LRR RLKs regulate the activity of downstream components through different downstream effectors to allow signaling transduction to take place in a scenario quite reminiscent to that in animals, such as transcriptional level of signaling molecules regulation or ubiquitin-mediated degradation and kinase activity to control the signal strength.

During the past decades, extensive studies on yeast and animal cells have revealed that protein-protein interactions via domain recognition provide a fundamental framework for signaling network assembly, which in turn controls the specificity of signaling transduction. Src homology-2 (SH2) and SH3 domain are the two well-studied modules for binding to receptor tyrosine kinases (RTKs) in animals (Pawson et al. 2001). These RTKs are activated by phosphorylation to recruit proteins containing SH2 domains for binding to the receptors, and subsequently regulate the activity of the downstream effectors. However, and different to animal cells, where a large population of the receptor kinases possess tyrosine kinase activity, most of the RLKs identified so far in plant are predicted to belong to the serine/threonine class of protein kinases. In recent years, the tyrosine phosphorylation site in plant RLKs has been detected and functions as an important regulator for the plant signaling transduction process, raising the question whether plants also use similar adaptors to animals for signaling regulation (de la Fuente van Bentem and Hirt 2009). Although SH2 and SH3 domain-containing proteins have been reported in plants, their exact role in which signaling pathway(s) has not yet been demonstrated experimentally. Here, we will discuss the evolutionary conservations of plant SH2 and SH3 domains and their potential functions in mediating plant signaling transduction. In particular, we will also discuss the roles of a plant SH3 domain-containing protein subfamily in regulating protein trafficking and organelle biogenesis.

2 SH2 Domain-Containing Proteins in Plants

As an evolutionary module, the SH2 domain usually contains 100 amino-acid residues and has multiple roles in regulating different cellular events (Pawson et al. 2001). The SH2 domain was first discovered in the Src tyrosine kinase protein and then found in many other adaptors or signaling related proteins. SH2 domain repeats contribute to the binding ability of SH2 domain to the phosphorylated substrates. In animal cells, signal transducers and activators of transcription (STATs) are other SH2 domain-containing members, which function as the second

messengers in the JAK (Janus kinase)-STAT pathway by selectively binding to a DNA sequence through their SH2 domain (Levy and Darnell 2002; Bromberg and Darnell 2000).

So far, based on sequencing blast and domain analysis, there are only several putative STAT type SH2 domain-containing proteins in Arabidopsis (Fig. 1). Based on the sequencing blast and comparisons using the SH2 domain of a *Dictyostelium* STAT protein, two SH2 domain-containing proteins are predicted (Williams and Zvelebil 2004) (Fig. 1a). However, their molecular functions are unreported.

In another study, two STAT-type SH2 domain proteins have been found in Arabidopsis and one in Rice (Gao et al. 2004) (Fig. 1b). Although they lack a DNA binding domain, in vitro pull down experiments have shown that one Arabidopsis STAT-type SH2 domain protein might be associated with a tyrosine-phosphorylated protein, implying that the SH2 module might have conserved roles in a tyrosine-dependent manner (Gao et al. 2004). Plant SPT6L (Suppressor of Ty insertion 6-like) proteins are predicted by secondary structural comparison to yeast SPT6 (Gao et al. 2004). They have been shown to control apical–basal polarity during embryogenesis in Arabidopsis (Gu et al. 2012). One notes that SPT6L also contains a putative WG/GW-repeat that is plant-species

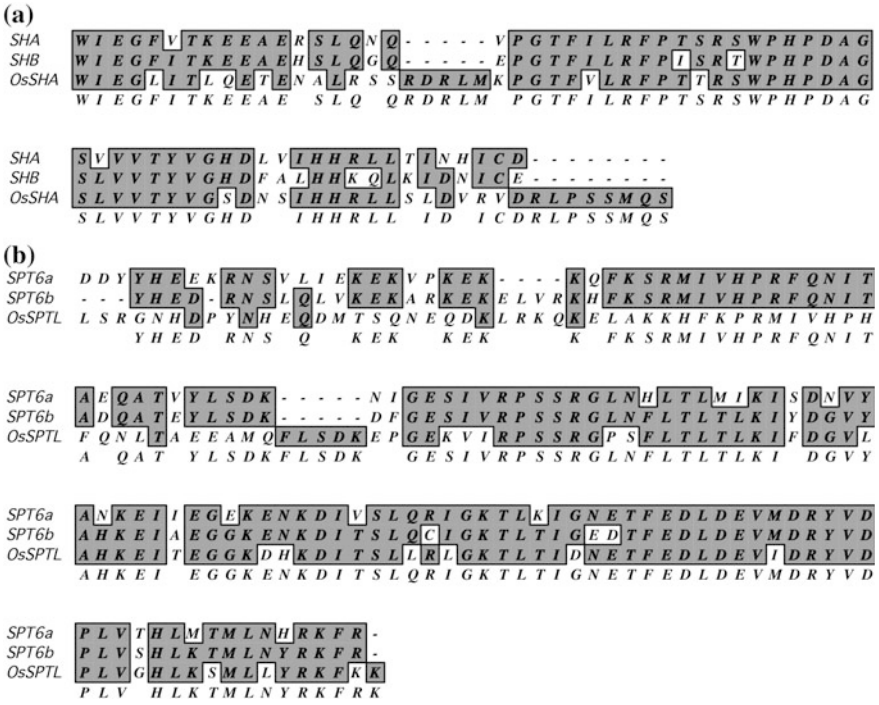

Fig. 1 Conserved SH2 domain-containing proteins in plants. **a** Sequence alignment of STAT type SH2 domain-containing proteins. **b** Sequence alignment of SPT6 type SH2 domain-containing proteins

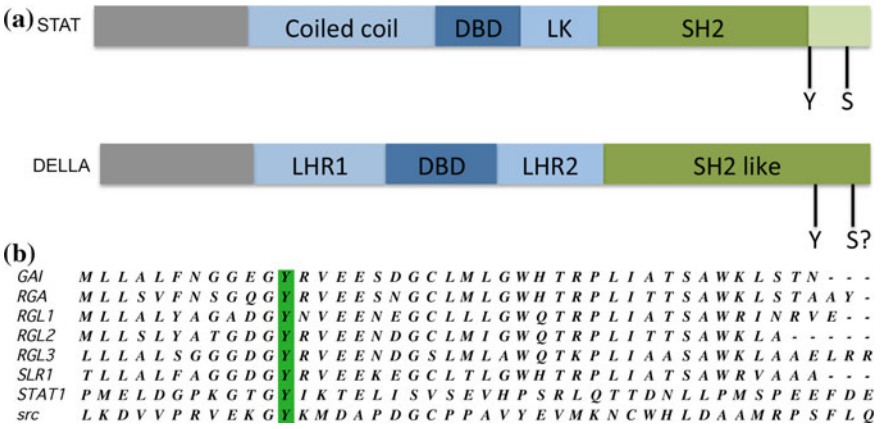

Fig. 2 Comparison of animal STAT and plant GARS. **a** GARS share similar domain structure to animal STAT. **b** Alignment of SH2 regions between STAT and GARS showing the conserved tyrosine kinases site among the STAT-like GRAS protein family

specific, although it is still unclear whether the SH2 domain contributes to this regulation.

Interestingly, a group of proteins called DELLA (Asp-Glu-Leu-Leu-Ala), which belongs to the subfamily of the plant-specific GRAS (named after GAI, RGA and SCR) regulatory protein family, also contain a highly conserved SH2-like domain in their C-termini (Richards et al. 2000; Hauvermale et al. 2012). The DELLAs proteins resemble STAT factors in that they contain two Leucine heptad repeat domains (LHR) and a SH2-like domain (Fig. 2). Recent studies have shown that these DELLA proteins regulate the activity of transcriptional regulators for gibberellin (GA) signaling (Zentella et al. 2007). The DELLA family in Arabidopsis comprises five homologs, including the repressor of ga1-3 (RGA), GA-insensitive (GAI), RGA-like1 (RGL1), RGL2, and RGL3 and one DELLA gene named SLR1 in rice (Hou et al. 2008). Although they share high homology in regard to their sequence and domain organization, genetic analyses have shown that these five homologs share overlapping and distinct functions during plant development. For example, both GAI and RGA are responsible for GA-induced vegetative growth and floral initiation, whereas RGL2 plays a more predominant role during GA-promoted seed germination (Hou et al. 2008; Lee et al. 2002; Tyler et al. 2004; Piskurewicz et al. 2008). In addition, it has been reported that DELLA proteins act as an integrator of multiple signaling pathways, such as auxin, abiotic stresses and plant pathogen responses (Yang et al. 2013; Gallego-Bartolome et al. 2011). These kinds of hormone and downstream effectors act in combination thus producing more varied responses than when acting individually.

3 SH3 Domain-Containing Proteins in Plants

The SH3 domain has been identified more than 30 years ago as a 60 amino acid segment shared among diverse signaling and cytoskeletal proteins of eukaryotes. The SH3 domain binds to its ligand via a proline-rich sequence, particularly those carrying the PxxP motif as well as other non-consensus ligands without the typical Pxxp motif (Saksela and Permi 2012). It is predicted that there are approximately 300 SH3 domain-containing proteins in animals, such the cytoskeleton proteins, the Ras proteins, and the Src kinase and many others, which regulate different cellular pathways (McPherson 1999).

Although the SH3 module has been extensively studied in yeast and animals and SH3 domain-containing proteins also exist in plants, relative little is known about the exact function of this scaffold adaptor in plant cells. Based on the known SH3 sequence blast, there are in total five proteins predicted to contain the SH3 domain in *Arabidopsis* and four in the rice genome (Fig. 3a, b). Interestingly, in plants, the

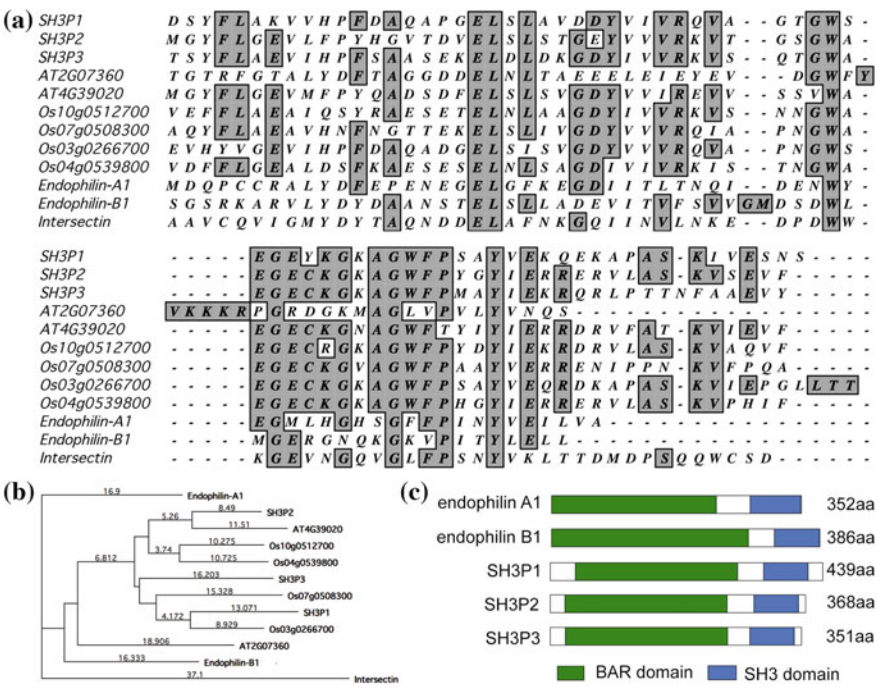

Fig. 3 Conserved SH3 domain-containing proteins in plants. **a** Arabidopsis and rice SH3-containing proteins were aligned with the SH3 domains of human endophilin A1, endophilin B1 and intersectin. Identical amino acids are indicated in the *gray* box. **b** Phylogenetic analysis of SH3 domain containing genes in plant and endophilin A1, endophilin B1, intersectin in animal. Results are predicted using Mac Vector. **c** AtSH3P proteins share similar domain organization to endophilin protein family with a N-terminus BAR domain and C-terminus SH3 domain

Table 1 Roles of AtSH3P protein family in plants

Protein	Domains	Membrane/ lipid binding ability	Interaction partner	Subcellular localization	Pathway	References
SH3P1	BAR, SH3	Yes	Auxilin-like protein; Actin	Clathrin-coated vesicles	Endocytosis	Lam et al. (2001)
SH3P2	BAR, SH3	Yes	ATG8; SH3P2	Autophagosome; Clathrin-coated vesicles?	Autophagy; Endocytosis	Lam et al. (2001), Zhuang et al. (2013), Zhuang and Jiang (2014)
SH3P3	BAR, SH3	Yes	ADL6	Clathrin-coated vesicles	Endocytosis, Vacuole degradation	Lam et al. (2001), (2002)

SH3 domain-containing proteins seem to belong to the same protein family that is involved in vesicle trafficking (Table 1). And notably, no SH3 domain-containing proteins have been found to be linked to the SH2 domain. One possible explanation is that during some conserved fundamental process such as vesicle trafficking that plant cells have also evolved evolutionally conserved molecules for regulation.

4 Roles of SH3 Domain-Containing Proteins in Clathrin-Coated Vesicle Formation

The SH3P subfamily constitutes the first reported SH3 domain-containing proteins in plants. In addition to the SH3 domain, they also contain a N-terminus coiled-coil domain that structurally resembles the N-BAR domain protein family (Fig. 3c), which are well known to function during membrane deformation events. Endophilins are one of the best-studied N-BAR subfamily in animal cells, and actively participate in vesicle trafficking pathways (Daumke et al. 2014; Frost et al. 2009). For example, during the clathrin coat mediated endocytosis pathway, endophilin A1 binds to the proline-rich domain of dynamin to promote vesicle scission and formation (Dawson et al. 2006; Frost et al. 2009).

SH3Ps contain three homologs, named as SH3P1, SH3P2, SH3P3 (Lam et al. 2001, 2002; Zhuang et al. 2013). Both SH3P1 and SH3P3 have been shown to be involved in clathrin-mediated pathways and subcellular studies have shown that SH3P1 is localized in the endomembrane system. Moreover, it is reported that SH3P1 interacts with auxilin, which may stimulate the uncoating of clathrin-coated vesicles (CCVs) together with Hsc70 (Krantz et al. 2013; Lemmon 2001; Ungewickell et al. 1995). SH3P1 may function as an inhibitor for the uncoating

event, whereas SH3P1 may function as a regulator or scaffold during the fission and the uncoating of CCVs (Lam et al. 2001). In addition, SH3P1 binds to actin via a non-SH3 region, implying its role in regulating cytoskeleton activity. In another study, it has been shown that SH3P3 cofractionated with a dynamin homolog ADL6 in plants (Lam et al. 2002). The dynamin ADL6 may participate in the CCV formation, as it has been shown to form a complex with several CCV components such as clathrin and γ-adaptin. Furthermore, other studies have shown that ADL6 is involved in protein trafficking from the *trans*-Golgi network to the vacuole but not to the plasma membrane (Jin et al. 2001; Lee et al. 2006). A potential PxxP motif has been identified in auxilin and ADL6, and deletion of the SH3 domain of either SH3P1 or SH3P3 abolishes the interaction, confirming that the SH3 domain is required for their binding. So far, it seems that these identified SH3 domain binding cargos are involved clathrin-mediated protein trafficking pathways. However, it appears that their preferential interacting partner(s) are involved in different subcellular events. For instance, SH3P1 interacts with auxilin to be involved in CCV-dependent endocytosis while SH3P3 associates with ADL6 and participates in vacuolar degradation. From sequencing alignment, they share very high identity (53 %) in the SH3 domain. Hence, it will be interesting for future studies to find out what causes their binding specificity, especially in terms of structural differences.

In addition to the biochemical data, information from mutant analysis is also needed to understand the specific roles of these SH3 domain-containing proteins during plant development and growth. During plant development, some conserved but fundamental machinery may be needed for some plant specific development process, such as seed germination and chloroplast development. It should be pointed out that ADL6 regulates gametophyte development in Arabidopsis, whereas mutation of ADL6 results in uncompleted cell plates and altered Golgi morphology (Backues et al. 2010). In regard to the association between ADL6 and SH3P3, genetic evidence for SH3 domain-containing proteins will be extremely useful for our understanding of the specific roles of the SH3 domain proteins in plants.

5 Roles of SH3P2 in Autophagosome Formation in Plants

Recently, our group has shown that one of the SH3 domain-containing proteins, SH3P2, participates in the autophagy pathway of plants (Zhuang and Jiang 2014; Zhuang et al. 2013). As a conserved cellular event, autophagy also occurs in plants cells to regulate the protein/organelle quality control and serve as an adaptive mechanism against unfavorable environmental conditions such as stress or pathogen infection (Li and Vierstra 2012; Liu and Bassham 2012; Hayward and Dinesh-Kumar 2011; Bassham et al. 2006; Floyd et al. 2012). Although the majority of autophagy related genes (*atg*) have been identified in the plant genome, the underlying mechanism as to how the autophagy pathway is regulated remains obscure. Based on sequence and domain comparison, we have found that SH3P2

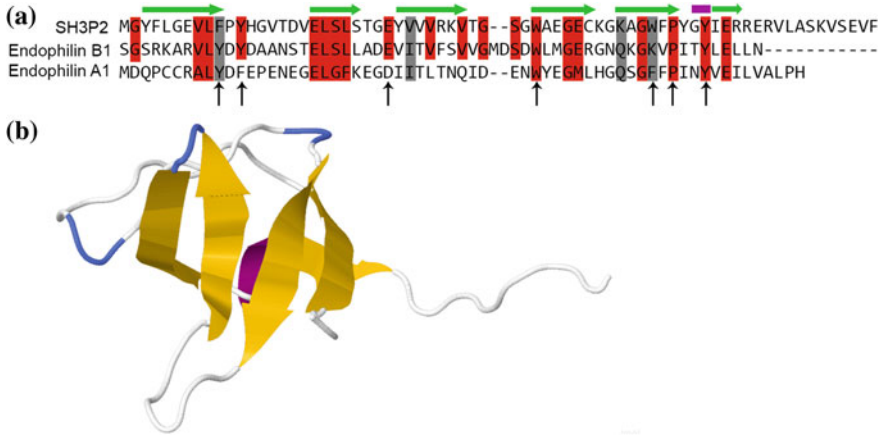

Fig. 4 Comparison of SH3 domain among SH3P2 and endophilin proteins. **a** Sequencing alignment of SH3 regions among SH3P2, endophilin B1 and endophilin A1. **b** A three-dimensional model of the SH3P2 SH3 domain based on endophilin B1

functions in a quite similar manner to endophilin B1 (also called Bif-1). In animal cells, Bif-1 was first found as an interactor of the Bax protein to control mitochondrial morphology (Etxebarria et al. 2009). Also, endophilin B1 is implicated to function during autophagy via an association with the PI3 K complex (Takahashi et al. 2007, 2008, 2009, 2011).

Sequencing alignment shows that SH3P2 shares high similarities to endophilin B1, but less to endophilin A1, especially in the SH3 domain region (Fig. 4a). SH3P2 and endophilin B1 share several conserved crucial functional residues (such as putative tyrosine phosphorylation site). Figure 4b shows a structural model for the SH3P2 SH3 domain predicted by using I-TASSER (Zhang 2008; Roy et al. 2010). The predicted SH3 secondary structural elements of SH3P2 fold into what might constitute a functional cargo-binding module. In animals, it has been shown that endophilin B1 interacts with UVRAG, which then forms a complex with the PI3 K complex. However, in plants a potential homolog has not been identified so far.

In our recent study, we have observed that SH3P2 is localized on the autophagosome membrane upon autophagy induction (Fig. 5). Immunoprecipitation studies demonstrated that SH3P2 forms a complex with the PI3 K components (Zhuang et al. 2013). In addition, we also found that SH3P2 interacts with the ATG8 members through its SH3 domain and the biological function of this interaction is still under investigation. It is possible that SH3P2 contains an ATG8 interacting motif (AIM) within the SH3 region. On the other hand, it should be pointed out that several studies have shown that the SH3 domain binds to ubiquitin, with an affinity comparable to the conventional SH3 ligand carrying the core PxxP sequence (Ortega Roldan et al. 2013; Stamenova et al. 2007; Trempe et al. 2009; Korzhnev et al. 2009). These subset of SH3 domain-containing proteins are involved in various pathways, and include the yeast endocytic protein Sla1, the

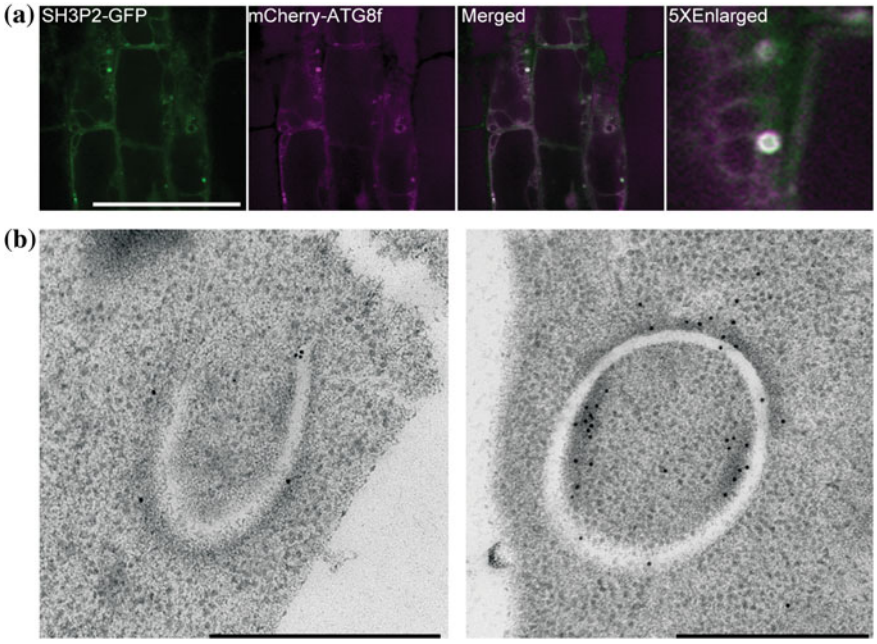

Fig. 5 Roles of SH3P2 in autophagosome formation in plants. **a** SH3P2-GFP translocated to autophagosome (mcherry-ATG8f) upon autophagy induction. Scale bar = 50 μm. **b** Electron microscopy analysis showing that SH3P2 is localized on autophagosome membrane indicated by anti-SH3P2 antibodies. Scale bar = 500 μm

mammalian amphiphysin protein and CIN85 protein. Ubiquitin and PxxP ligands may compete for binding to SH3 domains to regulate different protein complexes assembly in response to different signaling pathways (Stamenova et al. 2007). It will be interesting to test whether the SH3 domain of SH3P2 binds to ubiquitin, which would then be recognized by the ubiquitin receptor and finally targeted by ATG8 for degradation, as it is shown that several ubiquitin receptors contain an AIM motif to be recognized by ATG8 (Svenning et al. 2011; Zhou et al. 2013; Nakatogawa et al. 2012; Yamaguchi et al. 2010; Noda et al. 2010).

Interestingly, we have also observed that SH3P2 displays a mitochondria-like pattern under normal conditions (Fig. 6a, unpublished data). However, after autophagy induction, mitochondria are sometimes surrounded with the signals of SH3P2-GFP, while the majority of the SH3P2-positive punctae remain separate from mitochondria (Fig. 6b, unpublished data). It is possible that SH3P2 may play additional role(s) in linking mitochondria and autophagosomes. In animal cells, Bif-1 has been implicated to participate in apoptosis and is required for the maintenance of mitochondrial morphology and dynamics (Takahashi et al. 2005, 2013a, b; Etxebarria et al. 2009). Therefore, based on the connection between SH3P2 and mitochondria, we cannot exclude the possibility that SH3P2 may also function during plant apoptosis or mitophagy.

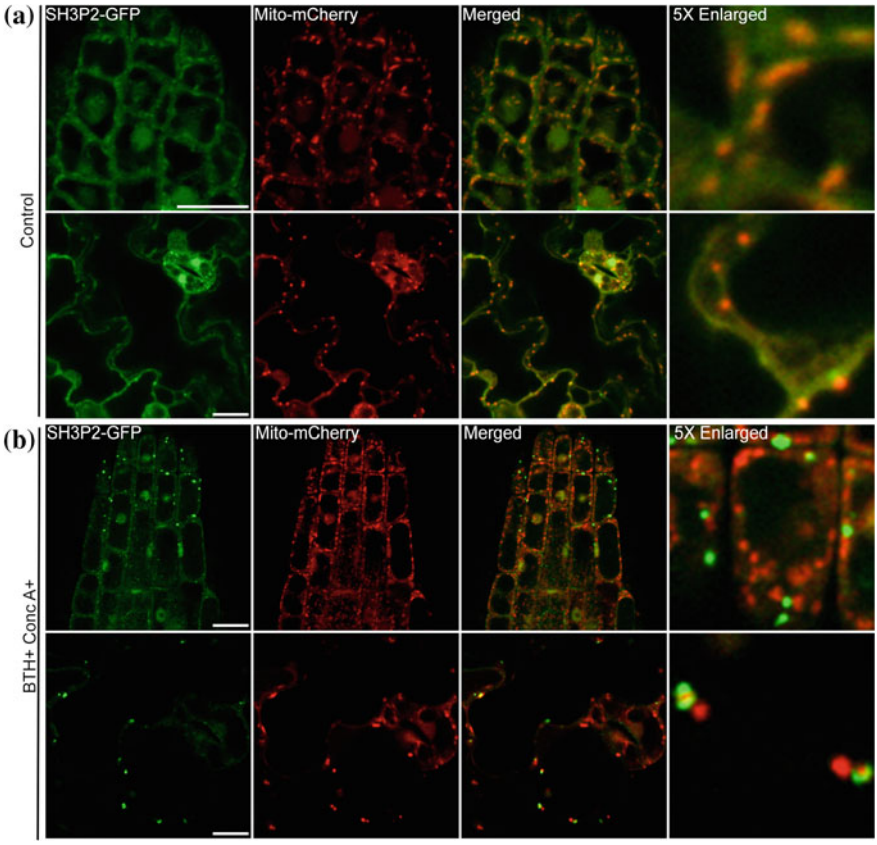

Fig. 6 Association of SH3P2 and mitochondria. **a** Transgenic Arabidopsis plants expressing SH3P2-GFP display a mitochondria pattern in root tip *top panel* and leaf *bottom panel* cells in normal condition. **b** SH3P2-GFP translocated to large punctae in root tip (*top panel*) and leaf (*bottom panel*) cells upon autophagy induction. Scale bar = 10 μm

6 Discussion and Perspective

Signaling transduction is a fundamental part of all eukaryotic cells that arose in evolution from the requirements to regulate cell division and proliferation, in which molecular modules are adapted to comprise multiple complexes for specific pathways. However, plants have a unique lifestyle and are dependent upon hormone regulation and light signaling transduction, which require fewer modules and may evolve plant specific molecules for signaling pathways. Therefore, it is not surprising to find that there are much fewer homologs of the signaling modules in plants.

Both SH2 and SH3 domains are well-known modules during signaling transduction and in animal cells a number of SH2 domain-containing proteins are

covalently linked to the SH3 domain and possess the protein tyrosine kinase activity. Only several SH2 domain-containing proteins are predicted in the plant genome and it seems that they only have a single repeat of the SH2 domain, while in animals most of the SH2 domain-containing proteins carry an additional SH2 domain repeat or are coupled to the SH3 domain. Although there is no typical tyrosine kinase present in plants, several studies have shown that some of the receptor-like kinases contain tyrosine phosphorylation sites which exert essential regulation roles on signaling transduction (Oh et al. 2009, 2010; Afzal et al. 2008; Lin et al. 2014; Hirayama and Oka 1992). However, no experimental evidence has been provided to show the direct interactions of these receptors and the SH2 domain-containing adaptors during a signaling process. Instead, plants have evolved another set of unique transcription regulators called DELLAs for similar regulation. These have a domain organization that is quite reminiscent to the STAT type SH2 domain-containing proteins in animals (Sun 2010; Richards et al. 2000; Yasumura et al. 2007). Although DELLA proteins share little sequence similarities to those SH2 domain-containing proteins in animals, they seem to be some conserved essential amino acids (e.g., tyrosine phosphorylation site) and functional domains (e.g., DNA binding domain) (Fig. 2a). This explains why the searching of a specific domain in a protein might be overlooked simply based on sequencing alignment, and during evolution some unconserved regions in the plant genome might have masked it. The DELLA protein family functions as a pivotal regulatory module for a wide range of core plant developmental process (Sun 2010; Pierik et al. 2007; Zentella et al. 2007). The plasticity of plant development and growth are largely dependent on hormone pathway regulation. In particular, different hormone pathways exhibit physiological redundancy and crosstalk with other(s). Evidence is accumulating which indicates that a transcription regulator is involved in multiple hormone pathways, thereby serving as integrators of multiple signals (Cui and Luan 2012; Depuydt and Hardtke 2011; Farquharson 2010; Peng 2009; Robert-Seilaniantz et al. 2011; Song et al. 2014). Therefore, this may also explain that why plants process fewer and less complicated transcription regulators. Also, these plant unique regulators may perform various roles in plant development. Recently, it has been reported that DELLA proteins direct bind to a tubulin-folding cochaperone called prefoldin in order to regulate the plant cytoskeleton (Dixit 2013; Locascio et al. 2013).

On the other hand, studies from the SH3Ps subfamily implies that in some fundamentally conserved cellular events such as vesicular trafficking and cytoskeleton movement, plants have acquired some conserved regulators for these basic activities (Fig. 7). The endomembrane system is conserved in plants and consists of compartments and trafficking components that are similar but also some which are specific to plants (Surpin and Raikhel 2004; Robinson et al. 2008). In yeast or animals, a number of SH3 domain-containing proteins have been reported and play essential roles in either signaling transduction or other cellular process. So far, only a few SH3-interacting proteins have been identified from pull down assays or yeast two hybrid analysis. These SH3 domain ligands are quite similar to those reported for the animal endophillin subfamily, which is also featured by the N-terminus

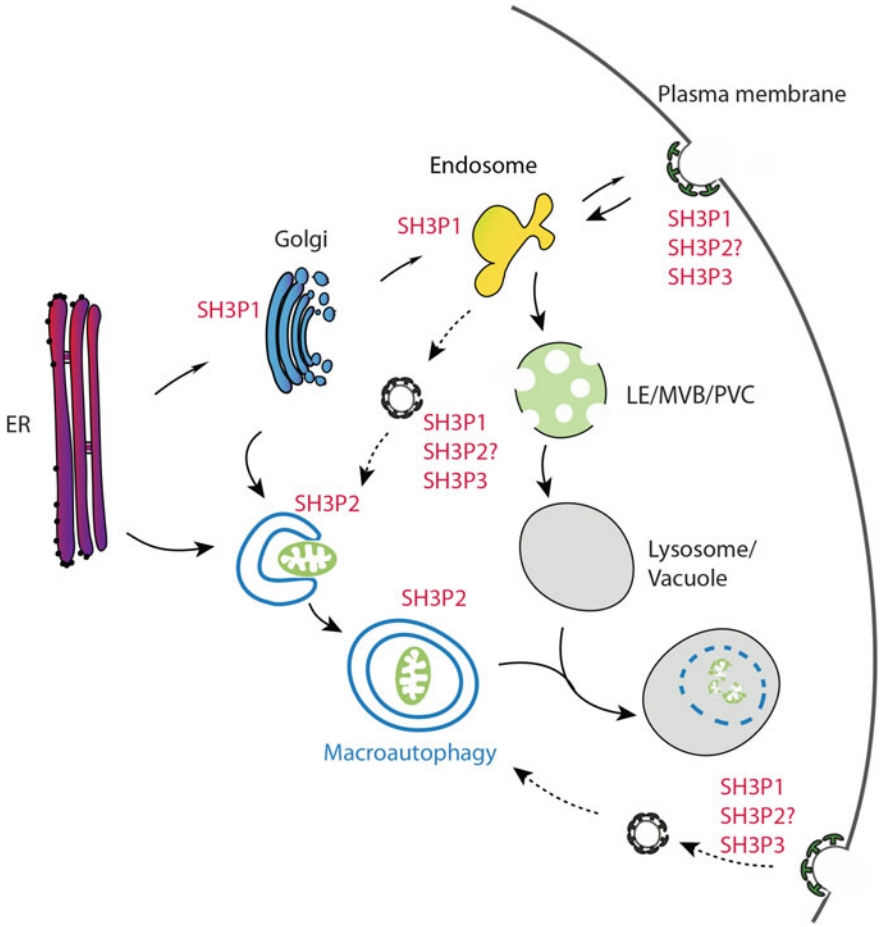

Fig. 7 Possible roles of SH3Ps in mediating membrane trafficking and autophagy in plants. Arabidopsis SH3Ps including SH3P1, SH3P2 and SH3P3 are involved in CCV formation. SH3P1 localizes in multiple endomembrane organelles/vesicles including Golgi, TGN, CCV and SH3P3 is related to CCV formation. Differently, SH3P2 is associated with mitochondria under normal condition and translocates to autophagosome membrane during autophagy

BAR domain. For example, SH3P1 binds to auxilin and actin, while SH3P3 may associate with dynamin in *Arabidopsis* (Lam et al. 2001, 2002). In animal cells there are various BAR and SH3 domain-containing proteins for different vesicle trafficking pathways. Our group has found that another SH3P homolog SH3P2 participates in autophagy in *Arabidopsis* (Zhuang et al. 2013). Although different SH3Ps are involved in distinct trafficking pathways, we also found that these SH3Ps may form homodimers or hetrodimers (unpublished data). These combinations of different homologs may facilitate the recruitment of downstream effectors for either temporal or spatial regulation. However, at the structural level, the detailed

interaction mechanism of these SH3 domains and their cargos have not yet been solved in plants, resulting in an unclear picture of the roles of these adaptor modules in the plant cell. Tools such as crystallography or nuclear magnetic resonance (NMR) will be needed in future to answer these questions, which may ultimately help us to better illustrate the specificity of these fundamental signal blocks in plant signaling pathways. Also, novel assays for the identification of the SH2/SH3 domain are needed to solve the complexity of protein sequencing during evolution. And more evidence at the experimental level is also needed for an understanding of domain-ligand interactions for plant development and growth.

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