Revisiting Apoplastic Auxin Signaling Mediated by AUXIN BINDING PROTEIN 1

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It has been suggested that AUXIN BINDING PROTEIN 1 (ABP1) functions as an apoplastic auxin receptor, and is known to be involved in the post-transcriptional process, and largely independent of the already well-known SKP-cullin-F-box-transport inhibitor response (TIR1) /auxin signaling F-box (AFB) (SCF<sup>AFB</sup>/SCF<sup>TIR1</sup>) pathway. In the past 10 years, several key components downstream of ABP1 have been reported. After perceiving the auxin signal, ABP1 interacts, directly or indirectly, with plasma membrane (PM)-localized transmembrane proteins, transmembrane kinase (TMK) or SPIKE1 (SPK1), or other unidentified proteins, which transfer the signal into the cell to the Rho of plants (ROP). ROPs interact with their effectors, such as the ROP interactive CRIB motif-containing protein (RIC), to regulate the endocytosis/exocytosis of the auxin efflux carrier PIN-FORMED (PIN) proteins to mediate polar auxin transport across the PM. Additionally, ABP1 is a negative regulator of the traditional SCF<sup>AFB</sup>-influenced auxin signaling pathway. However, Gao et al. (2015) very recently reported that ABP1 is not a key component in auxin signaling, and the famous abp1-1 and abp1-5 mutant Arabidopsis lines are being called into question because of possible additional mutation sites, making it necessary to reevaluate ABP1. In this review, we will provide a brief overview of the history of ABP1 research.

INTRODUCTION

The hormone auxin regulates many aspects of plant growth and development in all life stages, so studying the molecular and genetic mechanisms of the auxin signaling pathways is important for understanding plant growth and development. To perceive the presence of this hormone, auxin receptors are required, and they play a critical role as the "vanguard" for auxin signaling pathway. Two different classes of auxin receptors have been found in plants: the TIR1/AFB and AUXIN/INDOLE-3-ACETIC ACID (AUX/IAA) co-receptors, which control the auxin-dependent transcriptional responses, and AUXIN BINDING PROTEIN 1 (ABP1) (Tomas et al., 2013). ABP1 has been known and studied for almost 40 years, but due to the lack of available abp1 mutants, the first two decades of research were focused on its molecular and biochemical nature, e.g., the study of auxin binding (Jones 1994; Woo et al., 2002). During that time, the subcellular localization of ABP1 puzzled many researchers due to obvious contradiction presented by the localization of its endoplasmic reticulum (ER) and its apoplast-based function (Barbier-Brygoo et al., 1991; Inohara et al., 1989; Jones and Herman, 1993; Tillmann et al., 1989). To this day, its mechanism of escape from the ER is still being studied (Xu et al., 2014) and not known in detail. In 2001, the first ABP1 mutant (abp1-1) was identified from Arabidopsis (Chen et al., 2001), which shed light on the long sought ABP1 signaling mechanism. Since then, several mutant lines have been generated and studied intensely, resulting in the identification of several key ABP1 downstream components, such as ROP6-RIC1 and ROP2-RIC4. But recently there were several findings that shake the whole established ABP1 signaling world, mainly from the identification of two ABP1 null mutants which had no any auxin-related phenotypes (Gao et al., 2015), and the speculation of other mutation sites from abp1-1 (Habets and Offringa, 2015) and abp1-5 (Ender et al., 2015), another Arabidopsis mutant line which was usually used by ABP1 studies. In this review, the recent findings and remaining questions regarding the study of ABP1 will also be summarized and discussed.

NATURE OF ABP1

Identification of ABP1

In 1972, auxin was shown to bind to particulate cell fractions, potentially to a protein from maize coleoptiles (Cross and Briggs, 1978; Hertel et al., 1972). Later, auxin-binding proteins (ABPs) were successfully identified from maize through either indirect methods, such as the immunological approach (Löbler and Klämbt, 1985) and Ca<sup>2+</sup>-promoted sedimentation (Shimomura et al., 1986), or direct methods, such as photoaffinity labeling (Jones and Venis, 1989). Maize ABP1 has a 603-base pair open reading frame that codes a 22 kDa protein; a signal peptide of 38 amino acids, which was expected to translocate ABP1 across the ER membrane; and a C-terminal KDEL sequence, which was thought to be a signal for ER lumen
retention (Inohara et al., 1989; Tillmann et al., 1989). The transgenic production of the model plant Arabidopsis thaliana is much easier than for maize, so to perform complementation analysis of ABP-related mutants, it was necessary to identify ABP from Arabidopsis. In 1992, Arabidopsis ABP1 (AT4G02980), the sole ABP gene in Arabidopsis, was identified, which is similar to its maize homolog, i.e., 22 kDa molecular mass, N-terminal signal peptide of 33 amino acids, and C-terminal KDEL sequence (Palme et al., 1992).

**Interaction between ABP1 and auxin**

At the time that ABP1 was sequenced, the relative changes in auxin responsiveness and the concentration of ABP1 were found to be correlated (Jones et al., 1989). An antibody against a short sequence of maize ABP1 (Arg-Thr-Pro-Ile-His-Arg-His-Ser-Cys-Glu-Glu-Val-Phe-Thr) was found to have an auxin-like function in hyperpolarizing the protoplast transmembrane potential (Venis et al., 1992), indicating that this region is essential for the binding of ABP with auxin. Together with the KDEL sequence, this region, which was later called Box A (Brown and Jones, 1994), is shared by all of the ABPs that have been identified from plants (Napier et al., 2002).

ABP1 can bind with auxin under physiological concentrations suitable for the activities of this hormone, and the ideal pH for binding is 5.0-6.0 (reviewed by Bertoša et al., 1996; Napier et al., 2002). The correlation between the growth-promoting effects of auxin and its binding affinity to purified ABP1 was also measured (Rescher et al., 1996), and the crystal structure of maize ABP1 was determined, which is a dimer as it is found in solution (Shimoura et al., 1986; Woo et al., 2002). Residues 26-148 fold into a β-jellyroll barrel formed by two antiparallel β-sheets, and the auxin binding pocket is deep and predominantly hydrophobic with a zinc ion at the bottom of the pocket. When auxin binds within the pocket, its charged carboxylate group binds the zinc, and its aromatic ring binds the hydrophobic residues (Woo et al., 2002). Two conformations can be adopted by ABP1. When the auxin is absent, the extended C-terminus of ABP1 is irregular in structure except for a short α-helix (residues 152-160) (Woo et al., 2002), and tryptophan 151 is pulled out from the binding site (Bertoša et al., 2008). However, binding with auxin induces tryptophan 151 to interact with the aromatic auxin group, and the C-terminus is not extended, resulting in a more rigid conformation (Bertoša et al., 2008). Because of the single disulfide between Cys2 and Cys155, the N-terminal extension (residues 1-25), which is also irregular apart from a short β-strand, might also be rearranged by the binding (Woo et al., 2002). The change in conformation between the auxin-free and auxin-binding forms could be the signal that induces the transmembrane ABP1 receptor protein to transfer the auxin signal into the cell.

**ABP1 localization puzzle**

In animal cells, the KDEL retention sequence is sufficient for retention in the ER lumen (Pelham, 1989), and for ABP1, the presence of both the signal peptide and the KDEL sequence indicate its localization in the ER. Indeed, more than 90% of maize ABP1 was shown to be localized in the ER (Jones and Herman, 1993). However, maize ABP1 could not be photolabeled to auxin in intact cells, and at the pH level of the ER lumen, its binding with auxin was not detectable (Tian et al., 1995). Additionally, an antibody against maize ABP1 could block the auxin-induced hyperpolarization of the plasma membrane (PM) of tobacco mesophyll protoplasts, and adding maize ABP1 to a medium bathing tobacco protoplasts enhanced the auxin effect (Barbier-Brygoo et al., 1991; Jones and Herman, 1993). These results indicated the possibility of the presence of ABP1 on the apoplast and PM, and the results of electron microscopic immunocytochemistry finally indicated that maize ABP1 could escape from the ER to the cell wall via the secretory system (Jones and Herman, 1993), proving that ABP1 and auxin act at the cell surface. By using immunogold histochemistry together with transmission electron microscopy and epifluorescence microscopy of ABP1-GFP, it was shown that approximately 22% of Arabidopsis ABP1 was secreted from the ER to the apoplast (Xu et al., 2014), but ABP1 has no transmembrane domain to anchor itself into the PM. The ABP1 C-terminal sequence can bind with a glycosylphosphatidylinositol (GPI)-anchored protein designated as C-terminal peptide-binding protein 1 (CBP1), which may inactivate the KDEL sequence to facilitate the escape of ABP1 from the ER, and the phospholipid tail of CBP1 may serve as an anchor to the PM (Paulick and Bertozzi, 2008; Shimomura, 2006; Tommas et al., 2010). Xu et al. (2014) identified the PM-localized transmembrane kinases (TMKs), which bind with ABP1 to transduce the auxin signal, but it is still not known if TMK itself can serve as the anchor for all of the ABP1 molecules. The exact mechanism of ABP1 escape and anchoring remains unknown.

**ABP1 SIGNALING PATHWAY**

**Available ABP1 mutants**

To study gene function, mutant lines are required, and to date, ABP1 mutants have been generated and studied by many groups (Table 1). Using these mutants, it is finally possible to elucidate the role that ABP1 performs in auxin pathway, but two newly-identified ABP1-null mutants, abp1-c1 and abp1-TD1, do not have any previously reported auxin-related phenotypes (Gao et al., 2015). This calls into question whether ABP1 is really an auxin receptor. Several explanations have been proposed: the previously identified abp1 mutants might be subject to off-target effects (Gao et al., 2015; Grones et al., 2015; Liu 2015), and the new abp1-c1 and abp1-TD1 may express undetectable levels of functional mutant ABP1 protein by either an alternative splicing or the expression of a truncated transcript (Habets and Offerings, 2015). Embryo lethal abp1-1 mutant might contain background mutations (Enders et al., 2015; Habets and Offerings, 2015; Liu, 2015) that mask the function of other auxin signaling components. The T-DNA insertion in embryonetheal abp1-1 may influence the upstream BELAYA SMERT/RUGOSA2 (BSM/RUG2) gene because the bsm mutant allele is also embryo-lethal (Habets and Offerings, 2015), and this is supported by the negative result in the complementation assay by ABP1 expression (Grones et al., 2015). These findings undermine the data got from abp1-c1 and abp1-TD1, but fail to explain the auxin-related phenotype of down-regulated mutants such as SS12S, SS12K and abp1-AS. Usually, that knockout a gene has no resulting phenotypes in Arabidopsis would be because there are other proteins functionally overlapping with it. This might also apply to ABP1, after the finding that new ABP1 null mutants have no phenotype and old ABP1 mutants are being suspected. It is quite possible that there are some other proteins that functionally overlap with ABP1. Regarding SS12S, SS12K and abp1-AS, they were raised from immunization and RNAi in Col-0 background (Braun et al., 2008), and the antibody and antisense RNA raised against ABP1 may also inhibit other auxin binding proteins with overlapping function with ABP1. Most recently, also in Col-0 background, the overexpression of ABP1 caused gain-of-function auxin-related phenotypes, which could be masked by point-mutations targeting the auxin-binding site of ABP1, sup-
porting the important role of ABP1 in auxin-mediated processes (Grones et al., 2015). It is possible that the overexpressed mutated ABP1 may occupy the binding site in SPK1 or TMK, preventing the wild type ABP1 from binding with them. Alternatively, the mutated ABP1 may form complexes with the wild type ABP1 or the functional homologues thus masking their function, since ABP1 has been known to form dimers to perform their function (Woo et al., 2002). This indicates that there may be other proteins functionally overlapping with ABP1 in Arabidopsis.

ABP1 signaling in leaves
It has long been reported that ABP1 is involved in leaf development. Overexpression of ABP1 in tobacco resulted in leaves with larger cells (Jones et al., 1998), and ABP1 repression in Arabidopsis caused severe epinasty, smaller epidermal cells, smaller surface area, a slower growth rate and a reduced number of epidermal cells (Braun et al., 2008). Additionally, both abp1-5, which contains a His94→Tyr missense mutation in the putative auxin-binding region, and the abp1-AS line showed reduced lobe formation that could not be rescued with an exogenous auxin treatment (Xu et al., 2010), implying that the leaf defects are the result of blocking the auxin signaling. Although abp1-5 is not 100% reliable because of additional mutation sites (Enders et al., 2015), but the pavement cell phenotypes were also got both from abp1-AS (Xu et al., 2010), from other newly-generated ABP1 mutant lines (Effendi et al., 2015), and from ABP1 overexpressing lines generated from Col-0 (Grones et al., 2015). Therefore the leaf pavement cell phenotypes seems indeed due to deviant expression of ABP1. The same phenotype has been observed from the yuc1 yuc2 yuc4 yuc6 quadruple mutant, which presents defective auxin biosynthesis (Xu et al., 2010). Interestingly, the rop2RNAI rop4-1 mutant and the pin1-1 mutant have also shown the same phenotype, which cannot be rescued by exogenous auxin (Xu et al., 2010), indicating that ABP1, ROP2/4, and PIN1 are involved in the same auxin signaling pathway required for normal leaf lobe development (Fig. 1). Furthermore, ABP1-mediated auxin signaling is related to the auxin-involved indentation process that requires ROP6 function (Xu et al., 2014).

Table 1. abp1 mutants and ABP1 overexpression or inducible lines

| Line name | Transgenic plant | Cell line/Plant line | Type | Used in studies (Representative) |
|------------|------------------|----------------------|------|---------------------------------|
| F652; F631 | Tobacco          | Cell line/Plant line | Overexpression | Jones et al., 1998 |
| MJ10B      | Tobacco          | Plant line           | Overexpression | Jones et al., 1998 |
| KDEL; HDDEL; KEQL; KDELGL | Tobacco | Plant line | Overexpression | Bauly et al., 2000 |
| abp1-1     | Arabidopsis      | Plant line           | Knockout (T-DNA insertion) | Chen et al., 2001; Effendi et al., 2013; 2015 |
| NAS1       | Tobacco          | Cell line (BY-2)     | Downregulation (RNAi) | Chen et al., 2001 |
| SS12S; SS12K | Tobacco    | Plant line (BY-2)    | Downregulation (Immunization) | David et al., 2007 |
| SS12S; SS12K | Arabidopsis    | Plant line           | Downregulation (Immunization) | Braun et al., 2008; Chen et al., 2012; 2014; Paque et al., 2014; Tromas et al., 2009; Xu et al., 2010; 2010; 2014; Xu et al., 2010; 2010; 2014 |
| AS9/ABP1AS/abp1-AS | Arabidopsis | Plant line | Downregulation (RNAi) | Effendi et al., 2013; Robert et al., 2010; Xu et al., 2010; 2010; 2014 |
| abp1-5     | Arabidopsis      | Plant line           | His94→Tyr missense mutation | Effendi et al., 2013; Robert et al., 2010; Xu et al., 2010; 2010; 2014 |
| ABP1-GFP   | Arabidopsis      | Plant line           | Overexpression | Chen et al., 2014; Robert et al., 2010 |
| ABP1KDEL-GFP | Arabidopsis | Plant line | Overexpression | Robert et al., 2010 |
| abp1/ABP1  | Arabidopsis      | Plant line           | Downregulation | Effendi et al., 2011 |
| abp1-c1    | Arabidopsis      | Plant line           | Loss-of-function (CRISPR) | Gao et al., 2015 |
| abp1-TD1   | Arabidopsis      | Plant line           | Knockout (T-DNA insertion) | Gao et al., 2015 |
| ABP1-H59A; ABP1-H59A/H61A; ABP1-R24K; ABP1-R24K/L27V; ABP1-Q48D; ABP1-T56V; ABP1-P57L; ABP1-F148L; ABP1-W152Y; ABP1-R24K/L27V; ABP1-T56V/P57L; ABP1-F148L/W152Y; ABP1-V66A; ABP1-F92L; ABP1-P103L; ABP1-Q155D | Arabidopsis | Plant line | Point-mutation | Grones et al., 2015 |

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their endocytosis, which is critical for plant development (Lin et al., 2012), and ROP2, through its effector protein RIC4, accumulates cortical actin microfilaments, which further inhibits the endocytosis of PIN1 (Nagawa et al., 2012). ROP6 binds and activates cortical microtubule (MT)-associated RIC1 (Fu et al., 2009), which subsequently activates the MT-severing protein katanin (KTN1) to promote MT reorganization. This results in the rapid reorientation of cortical TMs, which destabilizes actin filaments instead of microtubules (Lin et al., 2013). Such an MT-severing protein has yet been found from root that directly interacts with ABP1 in root (Tromas et al., 2009). The D-type CYCLIN/RETINOBLASTOMA (RB) pathway, which is known to control G1/S transition during cell division (de Jager et al., 2009), and PLETHORA (PLT), which is required for root stem cell maintenance (Galinha et al., 2007), were found acting downstream of ABP1 in root (Tromas et al., 2009). However, unlike in leaf pavement cell, no transmembrane protein has yet been found from root that directly interacts with ABP1. Instead, SPK1, a transmembrane protein, was proposed to interact with an inactive form of ROP6 (Fig. 2) (Lin et al., 2012). Compared to the leaf pavement cell, the root requires higher auxin concentrations to inhibit endocytosis, and the ROP6-RIC1 pathway inhibits PIN2 internalization through the stabilization of actin filaments instead of microtubules (Lin et al., 2012). However, how the leaf MT regulator RIC1 affects the dynamics of actin in the root remains unclear (Nagawa and Yang, 2014). The ROP6 effector RIC1 also interacts with the RETINOBLASTOMA (RBP) pathway, which is known to control G1/S transition during cell division (de Jager et al., 2009), and PLETHORA (PLT), which is required for root stem cell maintenance (Galinha et al., 2007), were found acting downstream of ABP1 in root (Tromas et al., 2009).

**ABP1 signaling in roots**

Soon after *ABP1* knockdown *Arabidopsis* lines were generated, it was found that knockdown of this gene (line *ABP1-AS*, *SS12K* and *SS12S*) caused a drastic reduction in root growth (60-80%), and the size of the root meristem was reduced to one-third compared to the wild type (Thomas et al., 2009). Other phenotypes, such as greater root slanting angle and tropism defects, were also observed from heterozygous *abp1-1* line (Effendy et al., 2011; 2015). The D-type CYCLIN/RETINOBLASTOMA (RB) pathway, which is known to control G1/S transition during cell division (Jager et al., 2009), and PLETHORA (PLT), which is required for root stem cell maintenance (Galinha et al., 2007), were found acting downstream of *ABP1* in root (Tromas et al., 2009).

However, unlike in leaf pavement cell, no transmembrane protein has yet been found from root that directly interacts with ABP1. Instead, SPK1, a transmembrane protein, was proposed to interact with an inactive form of ROP6 (Fig. 2) (Lin et al., 2012). Compared to the leaf pavement cell, the root requires higher auxin concentrations to inhibit endocytosis, and the ROP6-RIC1 pathway inhibits PIN2 internalization through the stabilization of actin filaments instead of microtubules (Lin et al., 2012). However, how the leaf MT regulator RIC1 affects the dynamics of actin in the root remains unclear (Nagawa and Yang, 2014). The ROP6 effector RIC1 also interacts with the conserved MT-severing protein katanin (KTN1) to promote MT reorientation (Chen et al., 2014), but how this activity is involved in PIN endocytosis is uncertain. The function of ROP3 in regulating the recycling of PIN1 and PIN3 back to the PM was recently studied (Huang et al., 2014), and interestingly, ROP3 was also required to maintain PLT1/PLT2 expression (Huang et al., 2014), which is consistent with a previous study (Thomas et al., 2009) and suggests that ABP1 may regulate the identity of root stem cells through ROP3. Gain-of-function of ROP6 increases
the inhibitory effect of ABP1 knockdown lines (SS12S and SS12K), indicating that the ROP6-RIC1 system acts downstream of ABP1 (Chen et al., 2012; reviewed by Ren and Lin, 2015). Although it is possible that SPK1 performs a role similar to TMK in the root, a direct interaction between ABP1 and SPK1 has yet to be determined. Additionally, the role of SPK1 in the ROP3 signaling pathway remains elusive. It is also quite reasonable to suggest that TMK1 might interact with SPK1 to regulate the ROPs (reviewed by Ren and Lin, 2015), and this is worth testing.

A reduced basal-to-apical shift of PIN1 and PIN2 in the root stele and cortex was observed in the Arabidopsis icr1 mutant (Hazak et al., 2010). Reduction in ICR1 transcription could cause aberrant cell division in the embryo at the globular stage (Hazak et al., 2010), downward-folded blades, a short primary root and increased lateral roots (Lavy et al., 2007). Meanwhile, ectopic expression of ICR1 resulted in leaf pavement cells that were not interdigitated and lobed (Lavy et al., 2007), which resembles the abp1 phenotypes (Braun et al., 2008; Chen et al., 2001; Tomas et al., 2009; Xu et al., 2014), spk1, nicl and pin2 (Lin et al., 2012) and suggests that ICR1 might also have a role in ABP1 signaling. ICR1 has been shown to physically interact with ROP6 and ROP10 and is required for PIN exocytosis (Hazak et al., 2010; Lavy et al., 2007), but the precise function of ICR1 in ABP1 signaling requires further study.

Because TMK was determined to be a transmembrane receptor in ABP1-mediated signaling in the leaf (Xu et al., 2014), SPK1 may also have a role in ABP1 signaling in the leaf. It is also possible that TMK plays the same or a similar role in the root as SPK1. Compared to the wild type Arabidopsis, the tmk mutant has a shorter root and reduced sensitivity to auxin treatment and lateral root induction (Dai et al., 2013), so it resembles the phenotypes of the ABP1 mutants ABP1AS, SS12K and SS12S (Tromas et al., 2009). This suggests a potential role for TMK in root ABP1 signaling, but further studies are required.

**ABP1 regulation at the transcriptional level**

Initial research using the abp1-1 plant line and the SS12S/SS12K cell line revealed that ABP1 is related to cell expansion (Chen et al., 2001) and cell division (David et al., 2007). It was already thought that there should be some overlapping pathway between ABP1 and traditional SCFTIR1/AFB signaling (Braun et al., 2008; David et al., 2007), but with the availability of inducible ABP1 knockdown Arabidopsis lines (Braun et al., 2008), it was finally possible to examine the influence of ABP1 on genes regulated by the SCFTIR1/AFB system. The inactivation of ABP1 in SS12K generally reduced the transcription of Aux/IAA genes (Braun et al., 2008), whose expression is known to be regulated by the E3 ubiquitin ligase complex SCFTIR1/AFB (Mockaitis and Estelle, 2008). Interestingly, compared to the wild type, a subset of the Aux/IAA genes in SS12K showed decreased auxin responsiveness in the shoot (Braun et al., 2008) but increased responsiveness in the root (Tomas et al., 2009), indicating that ABP1 plays a different role in these two organs.

Using a heat-shock-inducible AXR3NT-GUS reporter, functional inactivation of ABP1 in SS12K degraded AXR3NT-GUS as an auxin output sensor, and the level of AXR3NT-GUS increased in a tir/afb mutant background, suggesting that ABP1 is a negative regulator of AUX/IAA degradation. ABP1 seems to increase the stability of AUX/IAA repressors, thus counteracting the SCFTIR1/AFB pathway (Tomas et al., 2013), and this counteraction could not be influenced by clathrin-dependent endocytosis inhibitors (ikarugamycin and tyrphostin A23), which indicates that it is independent of ABP1-regulated endocytosis (Tomas et al., 2013). Other ABP1 functions, such as cell wall remodeling, also occur via the control of AUX/IAA stability by ABP1 (Paque et al., 2014).

### CONCLUSIONS

ABP1 has been studied for decades, but many questions remain to be answered. ABP1 is predominately localized in the ER, and just a small amount can be secreted out (Jones and Herman, 1993; Xu et al., 2014). What is the function of ABP1 within the ER lumen? How does ABP1 escape KDEL retention to get into the apoplast? Unlike other PINs, PIN5 localizes to the ER, possibly regulating the flow of auxin from the cytosol to the ER lumen (Mravec et al., 2009), so would ABP1 regulate PIN5 to modulate intracellular auxin distribution as it does the ER lumen?
other PINs? Does auxin-free ABP1 also have a function? To date, only one transmembrane protein, TMK, has been identified as an ABP1 receptor (Xu et al., 2014), so are there any other membrane-localized receptor proteins that are required to perform these broad functions? The proteins that functionally overlap with ABP1 remains to be identified.

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