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REVIEW

The B subfamily of plant ATP binding cassette transporters and their roles in auxin transport

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Abstract

The ATP binding cassette B/multidrug-resistance/P-glycoprotein (ABCB/MDR/PGP) subfamily is a member of the ABC protein family. Significant progress has been made in the functional characterization of *ABCB* genes, particularly in *Arabidopsis thaliana*. This review evaluates recent advances concerning the plant ABCB subfamilies including their evolution and structure, the involvement and regulation of ABCB-mediated auxin transport, and the roles of ABCBs in plant growth and development. Insights into specific functions of members of the ABCB subfamily and their mediation of various regulatory pathways are also presented.

Additional key words: ABC protein family, gene expression, phylogenetic tree, subcellular localization, transgenic plants.

Evolution and structure of ABCBs

The ATP binding cassette (ABC) transporter family is very large and widespread in all organisms. On the basis of sequence similarity, protein size, orientation (forward or reverse pattern), and the presence or absence of idiotypic transmembrane and/or linker domains, the plant ABC proteins can be divided into eight subfamilies (ABCA - ABCH) according to Verrier *et al*. (2008), who introduced systematic nomenclature for plant ABC proteins. The ABCB subfamily, which is the subject of this review, is the second largest ABC protein subfamily in plants.

The availability of the complete genome sequences of some model plants (www.phytozome.net) has provided us with the opportunity to detect *ABCBs* in the plant kingdom. There are 10, 18, 21, and 22 putative *ABCB* genes in *Physcomitrella patens* (a moss), *Selaginella moellendorfii* (a fern), *Arabidopsis thaliana* (a dicotyledon) and *Oryza sativa* (a monocotyledon), respectively (Fig. 1; *OsABCB17* is not shown in the tree). The phylogenetic analysis of *ABCBs* in these four species indicates that the ABCB family genes can be divided into four clades belonging to four large lineages. In clades 1, 2, and 3, members of the ABCB family exist in all 4 species suggesting that these ABCBs have an ancient common ancestor that preceded the emergence of moss. However, only members of ABCBs in *Oryza sativa* are present in clade 4. ABCBs of lower plants (*Physcomitrella patens* and *Selaginella moellendorfii*) are found in several different locations, often as sisters to angiosperm (*Arabidopsis* and *Oryza sativa*) clades that subsequently show the monocot/dicot split. In addition, there are more ABCBs in angiosperms than in the lowerd plants suggesting that an expansion of the *ABCB* gene family occurred to help plants adapt to environmental

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Abbreviations: ABC - ATP binding cassette; ABCB - ATP binding cassette B; AUX1/LAX - AUXIN RESISTANT1/LIKE AUX1; MDR - multidrug-resistance; NBDs - nucleotide-binding domains; NPA - 1-naphthylphthalamic acid; PGP - P-glycoprotein; phot1 - PHOTOTROPIN 1; PID - PINOID; PIN1 - PINFORMED1; TMDs - transmembrane domains; TWD1 - immunophilin-like FKBP42 TWISTED DWARF1.
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changes that occurred during the early evolution of plants (Fig. 1).

Plant *ABCB* genes have relatively large open reading frames which encode 125 - 140 kDa proteins (Jasinski *et al.* 2003). These proteins consist of two hydrophobic transmembrane domains (TMDs) containing six membrane-spanning α-helices and two nucleotide-binding domains (NBDs) involved in ATP binding. One TMD is fused with one NBD to form a TMD-NBD unit which is linked to another homologous TMD-NBD unit by a flexible linker domain consisting of ~60 amino acids. All four core domains are contiguous on a single polypeptide in a "forward" TMD1-NBD1-TMD2-NBD2 orientation (Ambudkar *et al.* 1999, Jasinski *et al.* 2003). This modular construction raises the possibility that various *ABCBs* can contribute to the binding and transport of different classes of compounds.

Computational modeling functionally characterizing ABCBs has shown that AtABCB4, AtABCB14, and AtABCB21 (but not AtABCB1 or AtABCB19) have N-terminal coiled-coil structures. The hydrophobic region of the fourth transmembrane helix in AtABCB4 is shifted below the membrane plane. The linker domain of AtABCB4 (but not AtABCB1, AtABCB14, AtABCB19, or AtABCB21) contains another coiled-coil structure. The substrate docking analysis of the three ABCB proteins (AtABCB4, AtABCB14, and AtABCB19) revealed two and three putative IAA binding sites in AtABCB19 and AtABCB4 TMDs, respectively, and nonspecific IAA docking in AtABCB14 TMDs (Yang and Murphy 2009). All of these results provide a reasonable explanation for the different functions of these proteins, as discussed below.

Table 1. The prediction of subcellular localization of ABCBs in rice. Locus IDs of genes from the *TIGR* rice genome annotation project database (http://rice.plantbiology.msu.edu)

Gene names	Locus IDs	Plasma membrane	Vacuolar membrane	Golgi apparatus	Endoplasmatic reticulum	Cytosol	Chloroplast
OsABCB1	LOC_Os01g18670	9	4				
OsABCB2	LOC_Os01g34970	8	3	2			
OsABCB3	LOC_Os01g35030	4	9				
OsABCB4	LOC_Os01g50080	8	3		2		
OsABCB5	LOC_Os01g50100	7	3	3			
OsABCB6	LOC_Os01g50160	10			3		
OsABCB7	LOC_Os01g52550	11	2				
OsABCB8	LOC_Os01g74470	11	1		1		
OsABCB9	LOC_Os02g09720	6				4	3
OsABCB10	LOC_Os02g21750	11.5			2	6.5	
OsABCB11	LOC_Os02g46680	10	2	2			
OsABCB12	LOC_Os03g08380	11					2
OsABCB13	LOC_Os03g17180	9	2		2		
OsABCB14	LOC_Os04g38570	10	1	2			
OsABCB15	LOC_Os04g40570	6				3	2
OsABCB16	LOC_Os04g54930	12				2	
OsABCB17	LOC_Os05g04610	5	2		2		3
OsABCB18	LOC_Os05g47490	10	2	2			
OsABCB19	LOC_Os05g47500	10		2			
OsABCB20	LOC_Os08g05690	13					
OsABCB21	LOC_Os08g05710	8	2	2			
OsABCB22	LOC_Os08g45030	3			2	8	

The function of ABCBs in auxin transport

The phytohormone auxin is involved in the regulation of basic growth processes, such as cell division and cell elongation, and this hormone exhibits pleiotropic, important effects in plants (Sandberg *et al*. 2005, Teale *et al.* 2006, Abel and Theologis 2010, Park *et al.* 2011). A wealth of molecular and genetic data has been generated in recent years on the mechanism of auxin transport, especially of auxin transporters, providing significant insights into the action of this versatile pathway. It is undoubtedly true that auxin entering basal tissues in plants (such as roots) from the apical regions (where the auxin synthesis occurs) is transported through the central tissues of the root toward the tip, where it is presumably combined with apically produced auxin (Ljung *et al*. 2005) and redistributed toward the flanks and then transported basipetally through the lateral root

cap and epidermis (Swarup and Bennett 2003). Such a process requires the actions of many genes including *PINFORMED1* (*PIN1*) which was the first gene identified as being involved in this process (Goto *et al.* 1987, Okada *et al.* 1991). In addition to the PIN proteins, AUXIN RESISTANT1/LIKE AUX1 (AUX1/LAX) and ABCB proteins also function in this auxin transport. Although there has been a great progress in elucidating this process in recent years, the role of ABCBs has only recently been a subject of study in plants.

The first two members of the ABCB family that were identified and associated with auxin transport were named AtPGP1 and AtMDR1 (later named AtABCB1 and AtABCB19). Their significance and functions were discovered through examining the similar phenotypes generated by the loss-of-function mutation in these genes; *atabcb19* and *atabcb19 atabcb1* double mutants have epinastic cotyledons, curled leaves, dwarf shoots and reduced apical dominance. These phenotypes suggest that these mutants have greatly impaired auxin transport activity (Noh *et al.* 2001). A more direct evidence for the participation of ABCBs in auxin transport was obtained in subsequent studies. For example, the free IAA content and basipetal auxin transport are severely reduced in *atabcb19* and *atabcb1* mutant hypocotyls and roots, and even more drastically reduced in the s*atabcb19 atabcb1* double mutant (Geisler *et al.* 2005). AtABCB1, AtABCB4, AtABCB19, and AtABCB21 proteins bind tightly and specifically to the auxin transport inhibitor 1-naphthylphthalamic acid (NPA) (Noh *et al.* 2001,

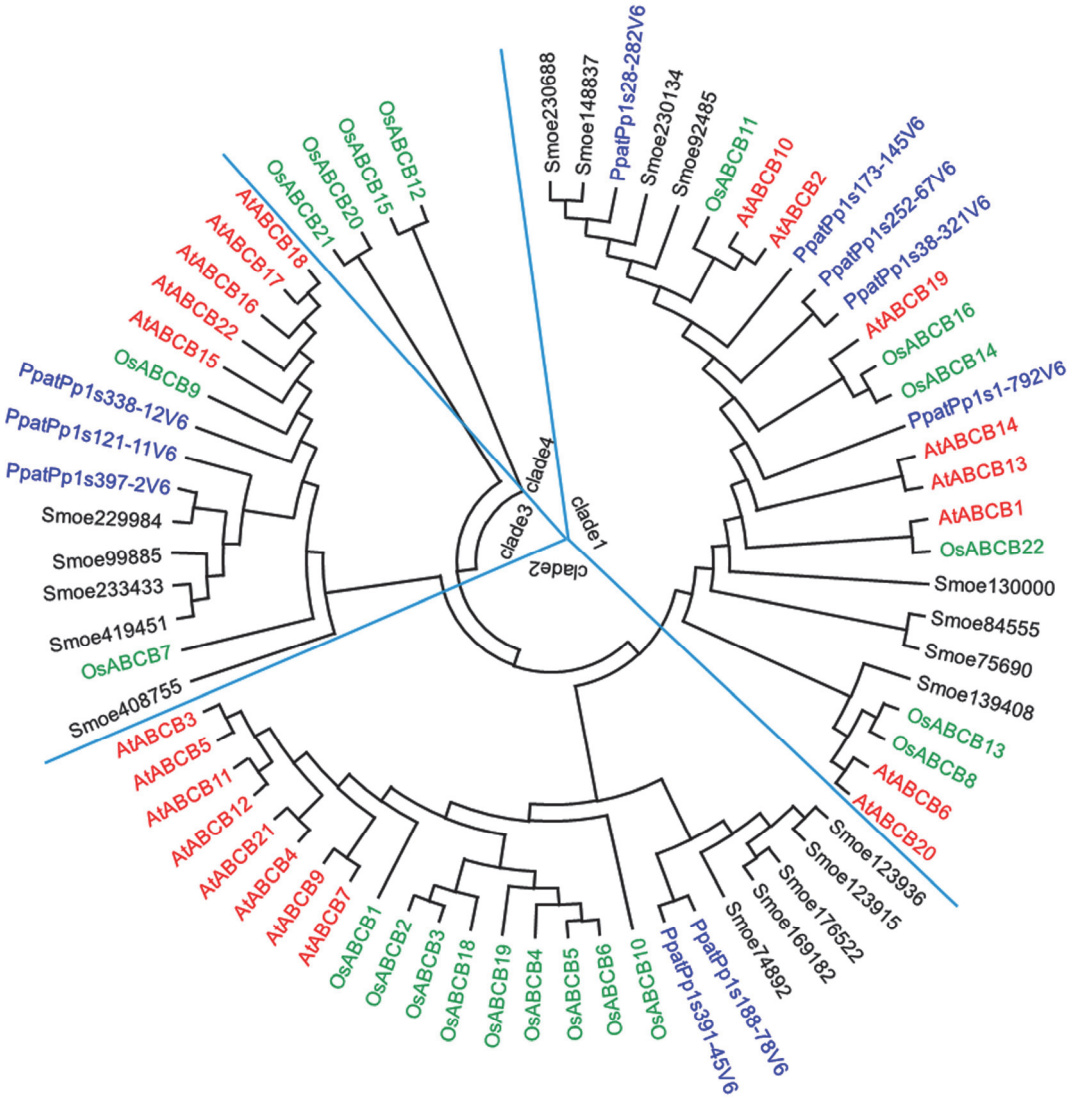

Fig. 1. The phylogenetic tree of ABCB proteins in four representative plant genomes. ABCB protein sequences were retrieved with family *BLAST* searches in the *Phytozome v. 8.0* database (www.phytozome.net). Predicted amino acid sequences were aligned using *ClustalX* and subjected to the phylogenetic analysis using the neighbor-joining method with *MEGA4* using 1 000 bootstraps. Ppat - *Physcomitrella patens*, Smoe - *Selaginella moellendorfii*, At - *Arabidopsis thaliana*, Os - *Oryza sativa*.

Murphy *et al.* 2002, Geisler *et al.* 2003, Terasaka *et al.* 2005, Kamimoto *et al.* 2012). The expression of AtABCB1, AtABCB4, AtABCB19, and AtABCB21 in yeasts, human MDR-type proteins (He-La), and *Arabidopsis* protoplasts results in altered efflux or influx of IAA (Geisler *et al.* 2005, Santelia *et al.* 2005, Terasaka *et al.* 2005, Bouchard *et al.* 2006, Petrásek *et al.* 2006, Blakeslee *et al.* 2007, Kamimoto *et al.* 2012). Takanashi *et al.* (2012) showed that LjABCB1, which is a homolog of the *Arabidopsis* auxin transporter AtABCB4, is specifically expressed during nodulation in *Lotus japonicus*. Auxin is closely involved in the development of nodule vascular bundles and in lenticel formation on the nodules of *Lotus japonicus* (Takanashi *et al.* 2011). All of these results strongly support the crucial role of ABCBs in auxin transport.

By taking the advantage of analysis using ^{3}H-IAA and ^{3}H-NAA, Geisler *et al.* (2005) found that the reduction in efflux of natural and synthetic auxins observed in mutant *atabcb1* protoplasts isolated from leaf mesophyll cells correspond well with the reduced transport observed in whole plants. At the same time, heterologous expression systems based on *Saccharomyces cerevisiae* and human HeLa cells were used to express and characterize AtABCB1, resulting in enhanced efflux of IAA and 1-NAA but not the inactive auxin 2-NAA. Similar results were reported for AtABCB19 (Bouchard *et al.* 2006, Petrásek *et al.* 2006, Blakeslee *et al.* 2007). These results indicate that ABCB1 and ABCB19 have auxin efflux directionalities in plant, yeast, and animal cells.

However, although ABCB4 shares a sequence similarity with both ABCB1 and ABCB19 (60 and 61 %, respectively), the results of the transport assay of AtABCB4 in HeLa cells and yeast are contrary to those of AtABCB1 and AtABCB19. These results suggest that AtABCB4 functions primarily in the uptake of auxin (Santelia *et al.* 2005, Terasaka *et al.* 2005). In a recent study, a root hair model based on the role of auxin as positive effector for root hair elongation (Okada and Shimura 1994, Schiefelbein 2000) was effectively used to analyze the roles of ABCBs in auxin transport (Cho *et al.* 2007). The criteria used to examine the roles of these proteins are: *1*) enhanced auxin efflux or reduced influx activity resulting in shorter root hairs, and *2*) enhanced auxin influx or reduced efflux activity resulting in longer root hairs. Using the root hair cell system in *Arabidopsis* and *Nicotiana tabacum*, the authors demonstrated that AtABCB4 can export auxin (Cho *et al.* 2007).

Why does AtABCB4 display opposite auxin transport directionalities in heterologous expression systems and in plants? In a more recent study, an accessible *Schizosaccharomyces pombe* system for comparative studies of plant transporters was developed and used to preliminarily solve this perplexing question. AtABCB4 shows an auxin uptake activity at low auxin concentrations and, conversely, an export activity at high auxin concentrations (Yang and Murphy 2009); the analysis of the uptake kinetics of AtABCB4 also supports this notion (Kubeš *et al.* 2012). In addition, AtABCB21, another member of the ABCB family in *Arabidopsis* and also a close homolog of AtABCB4, has been identified as facultative auxin transporter, as AtABCB4 (Kamimoto *et al.* 2012). Therefore, ABCB family members have different auxin transport directionalities. More molecular and biochemical tools need to be employed and more ABCB family members need to be characterized to further elucidate the mechanism of ABCB-mediated auxin transport.

Highly tissue-specific expression and subcellular localization largely determine the specific developmental roles of ABCBs in plants. For instance, AtABCB1 is expressed in all suspensor cells and proembryonic cells, whereas AtABCB19 is restricted to suspensor-forming cells (Mravec *et al.* 2008). This pattern largely determines the functions of both ABCBs in auxin transport during the early stages of proembryo formation. AtABCB1 is localized in all root cells, except for the columella (Mravec *et al.* 2008), whereas AtABCB19 is restricted to the endodermis and the pericycle, and AtABCB4 is distributed in the epidermis and the lateral root cap (Wu *et al.* 2007). This localization pattern may contribute to the separate acropetal and basipetal auxin fluxes (Fig. 2). It is noteworthy that the complementary expression patterns of AtABCB19 and AtABCB4 (endodermis and pericycle *vs*. epidermis) fit well with their complementary functions (acropetal *vs*. basipetal auxin transport) indicating that members of the ABCB family can have complementary functions. AtABCB19 is highly expressed in the leaf primordia which is consistent with its role in cotyledon expansion (Lewis *et al.* 2009). AtABCB14, which was observed in the plasma membranes of guard cells, modulates stomatal responses to CO_2 (Lee *et al.* 2008). We predicted the expression profile of rice ABCBs in roots at different developmental stages and in different tissue types using *RiceXPro v. 1.6* (http://ricexpro.dna.affrc.go.jp/ RXP_4001/index.php) (Fig. 2). OsABCB14 - 16 and OsABCB18 are expressed in the stele of the division zone, whereas OsABCB1, OsABCB4, OsABCB6, OsABCB9, OsABCB17, and OsABCB22 are localized in the stele of the elongation zone, and OsABCB7, OsABCB10, OsABCB11, and OsABCB13 are expressed in the stele of the maturation zone. All of these *ABCB* genes may share similar functions. However, OsABCB2, OsABCB5, and OsABCB8 are localized in the cortex of the elongation zone, the root cap, and the epidermis of the maturation zone, respectively. These proteins may function in different processes. We also predicted the subcellular localization of these ABCBs using http://wolfpsort.org/ (Table 1). The 22 rice ABCBs are nearly all localized in the plasma membrane; however, OsABCB3 and OsABCB22 are localized in the vacuolar membrane and the cytosol, respectively.

However, as ABCBs are linked to auxin transport,

polarity, which seems to be unique to auxin within plant tissues (Petrášek and Friml 2009), may be at the heart of ABCBs function. In general, members of the ABCB family exhibit polar and apolar subcellular localizations in apical tissues, and polar localization in mature tissues (Bandyopadhyay *et al.* 2007).

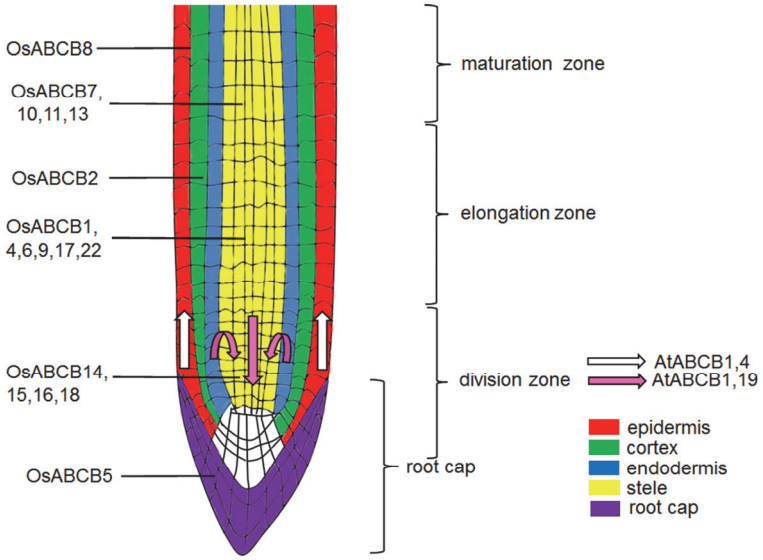

Fig. 2. *Arabidopsis* ABCB-mediated auxin transport streams in the apex of the primary root, and predicted tissue-specific localizations of rice ABCB proteins in the primary root. The primary root is divided into the root cap and division, elongation and maturation zones whose regions are approximately marked with curly brackets. For the maturation zone, only the basal (elongation zone-facing) side was diagrammed. For predicted tissue-specific localizations of rice ABCB proteins in the primary root, only the localization exhibiting the strongest expression was selected for every ABCB. We found no data concerning OsABCB3, OsABCB12, or OsABCB19-21 in *RiceXPro version 1.6*. The *lines* represent expression and the *arrows* represent function.

Factors regulating ABCB-mediated auxin transport

ABCB-mediated auxin transport is regulated at many different levels including the regulation of transcription, transport activity, subcellular trafficking (endocytic recycling and polarized targeting), protein-protein interactions, and phosphorylation **(**Tanaka *et al.* 2006, Vieten *et al.* 2007, Titapiwatanakun and Murphy 2008, Petrášek and Friml 2009**)**. Auxin itself alters the transcription of ABCBs (Noh *et al.* 2001, Terasaka *et al.* 2005). Most studies have focused on *AtABCB1*, *AtABCB4*, and *AtABCB19* which are upregulated by auxin application (Noh *et al.* 2001, Geisler *et al.* 2005, Terasaka *et al.* 2005). Studies of the responses of ABCBs to auxin treatment have indicated that *ABCB1* responds rapidly to auxin treatment (Geisler *et al.* 2005), whereas *ABCB4* may be a late auxin-response gene (Terasaka *et al.* 2005). Other phytohormones and abiotic stressors, such as brassinosteroids, abscisic acid, gibberellic acid, jasmonate, salicylic acid, salinity, drought, dark, and cold, also influence ABCB expression (Terasaka *et al.* 2005, Shen *et al.* 2010).

Some synthetic compounds, such as auxin transport inhibitors and endogenous flavonoid regulators, can regulate the transport activity of ABCBs. Multiple reports have shown that AtABCB1, AtABCB4, and AtABCB19 proteins bind to the auxin transport inhibitor NPA, thereby inhibiting their activities, and that these ABCBs are required for the proper transport and distribution of auxin from the sites of synthesis (Noh *et al.* 2001, Murphy *et al.* 2002, Geisler *et al.* 2003, Terasaka *et al.* 2005). There is some evidence that ABCB proteins are also regulated by some natural polyphenols, such as kaempferol, quercetin, and genistein. In both mammals and *Arabidopsis*, ABCBs interact with these compounds and bind to them (Ferte *et al.* 1999, Murphy *et al.* 2002). Flavonoids act as negative regulators of auxin transport in plant tissues where *ABCBs* are expressed (Ferte *et al.* 1999, Murphy *et al.* 2000, Brown *et al.* 2001, Peer *et al.* 2001, 2004). AtABCB1, AtABCB4, and AtABCB19, which are the best-studied examples of the ABCB family in *Arabidopsis*, are all inhibited by flavonoids in HeLa cells (Geisler *et al.* 2005, Terasaka *et al.* 2005). Flavonoids also disrupt interactions between ABCB1 and the immunophilin-like FKBP42 TWISTED DWARF1 (TWD1) (Bailly *et al.* 2008). A study using the *tt4* mutant and *abcb4* mutant suggests that flavonols regulate ABCB4 function in ways relevant to the mechanism of gravitropism, and that ABCB4 is regulated by products of the chalcone synthase enzyme (Lewis *et al.* 2007). However, the mechanism of action of these compounds is not yet fully understood.

The polarity of auxin transport can be modulated by changes in the subcellular localization of PINs within each auxin-transporting cell (Wisniewska *et al.* 2006). How the direction of auxin flow is controlled by polar localization of ABCBs is unclear, but it is reasonable to assume that their asymmetric localization patterns may also have a functional meaning. Several lines of evidence indicate that, like their mammalian counterparts, *Arabidopsis* ABCBs are regulated *via* endocytosis (Blakeslee *et al.* 2005). For example, the association of ABCBs with a number of proteins, such as ADL1A, patellin1, β-adaptin, and TWD1 provides direct evidence for ABCB trafficking in plants (Murphy *et al.* 2002, Geisler *et al.* 2003, Wu *et al.* 2010). Additionally, when treated with the membrane trafficking inhibitor brefeldin A, ABCB4 is partially and reversibly disturbed (Cho *et al.* 2007), and ABCB1 aggregates in intracellular bodies with PIN2 (Blakeslee *et al.* 2007, Titapiwatanakun *et al.* 2008) suggesting that these ABCBs are readily regulated *via* endocytic cycling. However, 3-(5-[3,4-dichloro-phenyl]-2-furyl)-acrylic acid (referred to as gravacin) also interferes with trafficking ABCB19 to the plasma membrane (Rojas-Pierce *et al.* 2007). This occurs despite the fact that ABCB19 is more stably situated on the plasma membrane than PIN-family proteins (Titapiwatanakun *et al.* 2008) and that ABCB19 appears to be trafficked by GNOM-LIKE1, a member of the large family of ARF guanine nucleotide exchange factors and a main regulator of the basal recycling pathway (Richter *et al.* 2007, The and Moore 2007). The discovery of a variety of additional mutants identified by their general auxin-related phenotypes that exhibit altered ABCB localization will shed light on the mechanism involved in ABCB targeting (as was the case of PIN).

It is clear that precise auxin transport requires all three types of auxin transporters (PIN, ABCB, and AUX1/LAX), but the exact contribution of each to auxin transport, and whether they have synergistic or antagonistic effects on each other, remain unresolved. Recent elegant studies have helped make progress toward answering these questions by confirming that PIN-ABCB interactions regulate auxin transport. ABCB19 stabilizes PIN1 in membrane microdomains of *Arabidopsis* and there are specific PIN-ABCB protein interactions (Noh *et al.* 2003, Titapiwatanakun *et al.* 2008). Genetic evidence has partially demonstrated that ABCBs colocalize with PINs in plant tissues, and *pin abcb* mutants exhibit additive and synergistic phenotypes. PIN-ABCB interactions appear to influence auxin transport activity in HeLa cells and in yeast (Blakeslee *et al.* 2007). When ABCB1 or ABCB19 is coexpressed with PIN1 in yeast and HeLa cells, these proteins exhibit a synergistic effect and auxin efflux increases, but the coexpression of ABCB1 or ABCB19 with PIN2 produces a contrary result. The coexpression of ABCB4 and PIN2 lead to enhanced auxin uptake, whereas the ABCB4 coexpression with PIN1 results in decreased auxin uptake (Murphy *et al.* 2005, Bandyopadhyay *et al.* 2007). These results together with data from experiments involving the overexpression of PIN and ABCB in *Arabidopsis* and tobacco Bright Yellow-2 (BY2) cells suggest that the PIN and ABCB protein families show coordinated but also independent contributions to auxin transport (Mravec *et al.* 2008). In addition, an additive effect is observed when ABCB4 is coexpressed with AUX1, whereas an opposite effect when AUX1 is coexpressed with ABCB1, with similar results obtained in both yeast and HeLa cells (Bandyopadhyay *et al.* 2007, Yang and Murphy 2009).

Several studies have focused on the interaction between ABCBs and TWD1, and the protein phosphorylation of ABCBs. ABCB1 activity is dependent on the TWD1-ABCB1 interaction. TWD1 also affects the PM abundance of ABCB (according to Wu *et al*. 2010) because mutations in TWD1 cause mislocalization of ABCB1, ABCB4, and ABCB19 to the ER instead of the PM. TWD1 interacts with the AGC kinase PINOID (PID) and directs phosphorylation of ABCB1 in a regulatory linker domain that alters ABCB1-mediated auxin transport activity (Geisler *et al.* 2003, 2004, Bouchard *et al.* 2006, Bailly *et al.* 2008, Wu *et al.* 2010, Henrichs *et al.* 2012, Wang *et al.* 2013). Indeed, a phospho-proteomics study of plasma membrane proteins revealed three possible sites in ABCB proteins that can be phosphorylated by protein kinases in *Arabidopsis* (Nuhse *et al.* 2004). As predicted, phosphorylation of ABCB19 by PHOTOTROPIN 1 (phot1), a plasma membrane serine-threonine protein kinase that functions in multiple blue-light responses, inhibits its efflux activity (Christie *et al.* 2011). PID specifically regulates ABCB1-mediated auxin efflux, depending on its kinase activity and phosphorylation, as mentioned above (Henrichs *et al.* 2012). Research on single and double mutants has shown that ABCB19 functions directly downstream of the photoreceptor kinase phot1 (Christie *et al.* 2011) and upstream of the far red photoreceptor phyA (Lin and Wang 2005). Another member of the ABCB family, ABCB4, may act downstream of products of the chalcone synthase (Lewis *et al.* 2007).

Roles of the ABCB family in plant growth and development

The range of processes in which members of the various subclasses of plant ABC transporters have been implicated encompasses xenobiotic detoxification, stomatal function, polar auxin transport, vascular development, lipid catabolism, alkaloid transport, disease resistance, and ion regulation (Martinoia *et al.* 2002, Klein *et al.* 2004, Lee *et al.* 2005, Rea 2007, Crouzet *et al.* 2013, Le Hir *et al.* 2013, Shitan *et al.* 2013, Zhang

et al. 2012). ABCBs, the second largest ABC protein subfamily in plants, play crucial roles in the control of many processes involved in key developmental events in plants. Most of what is known about the roles that ABCBs play in plant growth and development has been revealed by studies of gain-of-function and loss-of-function mutants for five different *ABCB* genes in *Arabidopsis* using reverse genetics. The phenotypes of these mutants are shown in Table 1 Suppl. Consistent with the supposition that ABCB proteins mediate auxin transport, nearly all of the mutant phenotypes (including epinastic cotyledons, curled leaves, dwarf shoots and reduced apical dominance) correspond to the influence of application or lack of auxin suggesting that ABCB proteins regulate tissue patterning, cell enlargement, and cell division.

In general, ABCBs function primarily in long-distance auxin transport and primary root, lateral root, and root hair elongations (Peer *et al.* 2011). However, ABCBs also function in response to radiation. Since the first report of the biochemical characterization of AtABCB1 (published in 1998), researchers have speculated that responses to radiation may be mediated in part through ABCB proteins, as plants harboring sense and antisense constructs for the expression of *AtABCB1* exhibit different degrees of hypocotyl elongation under irradiance than in the dark (Sidler *et al.* 1998). In addition, Lin and Wang (2005) showed that AtABCB1 and AtABCB19 regulate photomorphogenesis in *Arabidopsis*, as the loss-of-function *atabcb1* and *atabcb19* mutants display hypersensitivity to far-red-, red-, and blue-radiation inhibition of hypocotyl elongation and abnormal expression of several light-responsive genes. Further evidence was provided by Christie *et al.* (2011), who demonstrated that ABCB19 can be phosphorylated by phot1 to inhibit its efflux activity, thereby achieving one step of the phototropic response. These results suggest that ABCBs function in response to irradiance by mediating polar auxin transport.

ABCBs also play an important role under stress conditions. The expression of many *ABCB* genes is suppressed or induced by stresses. AtABCB14, which is expressed mainly in guard cells and is localized at the plasma membrane, is both a malate uptake transporter and a negative regulator of CO_2-induced stomatal closure. CO_2-induced stomatal closure in detached leaves is slightly accelerated in *atabcb14* mutants and reduced in AtABCB14-overexpressing plants. Additionally, the flowering times of overexpressing plants are later than those of knockout mutants under normal growth conditions; this difference is more pronounced under elevated CO_2 concentration and drought (Lee *et al.* 2008) suggesting that AtABCB14 plays an essential role under stress. ABCBs also function in metabolite transport (Shitan *et al.* 2003), aluminum tolerance, and calcium homeostasis (Sasaki *et al.* 2002). Thus, like the other members of the ABC family, ABCBs have a wide range of functions.

Conclusions and perspectives

In recent years, genetic and biochemical approaches have revealed a wealth of information about the ABCB family members including their structure, regulatory factors, and function in growth and development. However, less is known about ABCBs in plants than in animals. To date, the functions of five genes of the ABCB family (*ABCB1, ABCB4, ABCB14, ABCB19*, and *ABCB21*) have been relatively well elucidated in the dicotyledonous model plant *Arabidopsis*, but the functions of most *ABCB* genes are unknown in monocotyledons and other dicotyledons. To our knowledge, only potato *PMDR1* (Wang *et al.* 1996), barley *HvMDR2* (Davies *et al.* 1997), wheat *TaMDR1* (Sasaki *et al.* 2002), maize *ZmBR2* (Multani *et al.* 2003, Knöller *et al.* 2010), sorghum *SbDW3* (Multani *et al.* 2003, Knöller *et al.* 2010), and *Coptis japonica CjMDR1* (Shitan *et al.* 2003) and *CjABCB2* (Shitan *et al.* 2013) have been cloned and partially characterized. It should be emphasized that although rice is a staple food for nearly one-half of the world population, to date there are no reports about rice ABCBs. It is reasonable to assume that ABCBs have similar and important functions among species, as do other ABC subfamilies, because they share similar sequences and structures.

Most research using *abcb* mutants has shown that ABCBs play critical roles in plant growth and development. However, the overlapping functions of members of the ABCB family make it difficult to reveal their real functions using single mutants. It is necessary to use double mutants for ABCB sister pairs or multiple mutants to determine the relationship between diverse *ABCB* genes. In the future, it would be interesting to perform the comparative analysis of the expression patterns and subcellular localizations of these genes and to construct multiple knockout mutants of ABCBs.

Recent evidence has also revealed a close inter-relationship between auxin stimuli and nutritional homeostasis (Liu *et al.* 2013). To a certain extent, the uptake and translocation of auxin and mineral nutrients are similar, as both processes require transporters. The movement of mineral ions is often mediated by multiple systems (Zazimalova *et al.* 2010). NRT1.1 was recently identified as dual-function auxin/nitrate transporter (Krouk *et al.* 2010). Thus, we speculate that there is an interaction and crosstalk between auxin and mineral nutrient transporters. The systematic transcriptome analysis of *abcb* mutants grown under different nutrient regimens, as well as research on the interaction between

ABCB and some other substances, and the upstream/ downstream regulation of ABCB will provide a basis for understanding the relationship between auxin and mineral nutrients.

However, it is not enough to elaborate the role of ABCB regulatory networks in various pathways. Thus, open questions to be answered by future studies include the identification of more *ABCB* genes, how (exactly) auxin is transported and regulated by a series of genes and proteins, how these factors cooperate and contribute to the auxin-mediated pathway, and how various pathways interact. We hope this review will inspire further research on the exact roles of ABCBs in the regulatory networks of auxin and other pathways.

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