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REVIEW ARTICLE

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Molecular players of auxin transport systems: advances in genomic and molecular events*

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ABSTRACT

Phytohormone auxin plays an indispensable role in the plethora of plant developmental process starting from the cell division, and cell elongation to morphogenesis. Auxins are transported to different parts of the plant by different sophisticated transporter molecules known as 'auxin transporters'.There are four auxin transporter families that have been reported so far in the plant kingdom which includes AUX/LAX (AUXIN-RESISTANT1–LIKES), PIN (PIN-FORMED, auxin efflux carriers), ABCB ((ATP-binding cassette-B (ABCB)/P-glycoprotein (PGP)) and PILS (PIN-Likes). Auxin influx and efflux carriers are distributed in a polar fashion in the plasma membrane whereas ABCB and PILS are present in a non-polar fashion. Other than AUX/LAX, other auxin transporters harbor N-and C-terminal conserved domains along with a variable hydrophilic loop in the transmembrane domain. The AUX/LAX, ABCB and PIN transporters mediate long distance auxin transport whereas PILS and PIN5 protein involved in intracellular auxin homeostasis.

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Auxin; influx carrier; efflux carrier; AUX/LAX; PIN; ABCB; PILS; transmembrane domain

1. Introduction

Auxin is one of the most important plant hormone that plays diverse roles in plants, starting from the cell division, differentiation and it's expansion to morphogenesis, organogenesis and vascular differentiation. The study of auxin biology dates back to the Darwinian era (1880) when Charles Darwin along with his son Francis Darwin performed the famous coleoptile experiments and reported about the movement of plants in response to an unknown factor 'influence'. They conducted this study in more than 40 plant species and described their findings in the book entitled 'The Power of Movement in Plants' (1881). The unknown factor was later named as 'auxin'. They predicted that auxin flow was basipetal i-e. directed-from the shoot apex towards the roots. Since then (post Darwinian era), it took around 100 years to identify the auxin transporters. The cell-to-cell directional flow of auxin requires both influx-and efflux carriers in the plasma membrane and other intracellular auxin carriers to maintain auxin transport and homeostasis within the cell. Without efficient communication between the cells, tissues and organs, evolution of complex functioning's in a multi-cellular organism is inconceivable. Due to the absence of mobile cells in plants, unlike animals, control of morphogenesis in plant is guided by chemical signals, commonly known as plant hormones. In recent times the auxin transport research has gained considerable attention and lots of advancements have been made in this field and also the role of auxin transporters in plant development has been dissected extensively at the cellular and molecular levels, which will be the focus of this review.

2. Auxin transporters

The phytohormone auxin is a non-polar solute and hence the transport of auxin across the membrane depends upon it's physio-chemical properties. Auxin (IAA) is a weak acid and present as IAA^+ (protonated) in its native state. The $pH_{,}$ of apoplastic cellular environment of IAA molecule is ranges in between 5 to 5.5 (Gout et al. 1992; Pin Ng et al. 2015) due to the presence of plasma membrane bound H^+ ATPases and at this $pH_{,}$ 83% of the IAA molecules remain in anionic (IAA^-, dissociated) and 17% (IAA^+, associated) in cationic form (Zažímalová et al. 2010). The negative charge (anion) of the IAA^- molecule prevents it to pass through the lipohilic plasma membrane and it only allows the protonated (cation) IAA^+ by passive diffusion (Zažímalová et al. 2010; Pin Ng et al. 2015). However, around 83% of the anionic IAA^- cannot pass though the plasma membrane and thus it requires auxin influx carriers to transport these molecules inside the cells. Further, after entering the cytosol, IAA encounters with the alkaline environment (pH 7 to 7.5) of the cell (Gout et al. 1992; Zažímalová et al. 2010; Pin Ng et al. 2015). The IAA remains in the anionic (IAA^-) form in the alkaline environment which makes it difficult to pass out of the cell, making the cell a weak anioinic chamber. To overcome this paradox, asymmetrical localization of auxin transporter molecules is required in different parts of the cell, to efflux IAA^- out of the cell. To facilitate the transport of IAA^- molecule, cells require specialized transporter molecules e.g. auxin efflux carrier (PIN) and ATP-binding cassette-B (ABCB)/P-glycoprotein (PGP)

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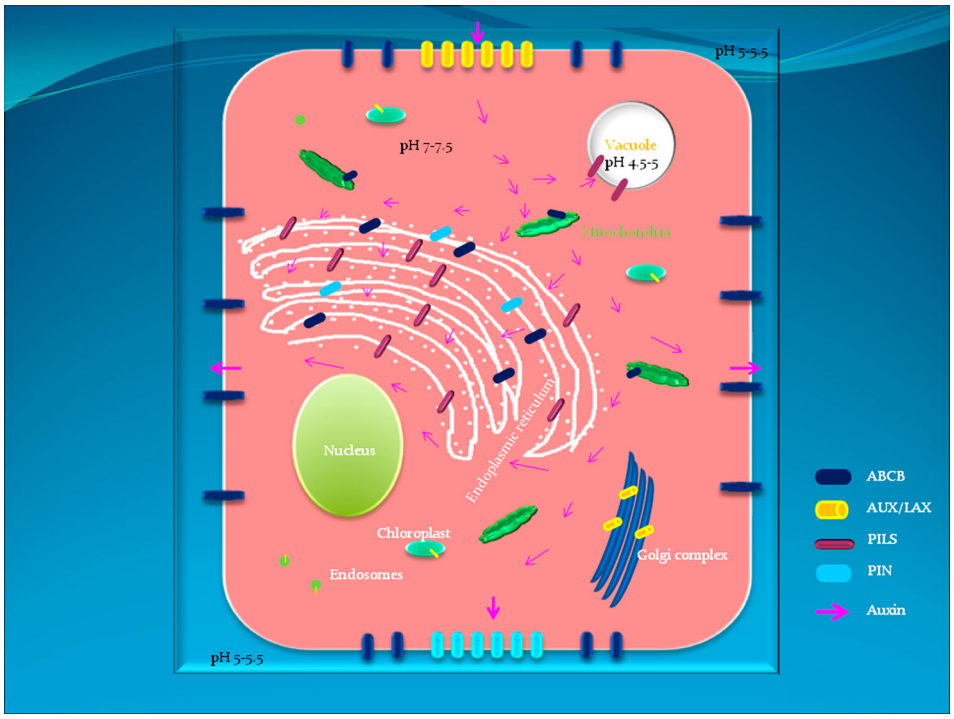

Figure 1. Pictorial representation of auxin transporters in the cell. PIN proteins are localized to the plasma membrane in a polarized fashion, whereas, AUX/LAX and ABCB are present in the plasma membrane and also in the sub-cellular compartments. PILS proteins are confined to the endoplasmic reticulum.

transporters (Friml et al. 2004; Terasaka et al. 2005). The cell-to-cell movement of auxin requires both influx and efflux carrier proteins in the plasma membrane and also in the intracellular spaces. The rate of non-polar auxin transport is about 5–20 cm/h whereas the rate of polar auxin transport is 5–20 mm/h (Michniewicz et al. 2007). To date, three major auxin transporters families have been reported which includes auxin influx carrier (AUXIN-RESISTANT1–LIKES (AUX1/LAX), PIN-FORMED (commonly known as an auxin efflux carriers, or PIN), and an ATP-binding cassette-B (ABCB)/P-glycoprotein (PGP). Recently identified auxin transporters from the intracellular spaces have been named as PIN-LIKES (PILS) (Barbez et al. 2012; Mohanta et al. 2015).

3. Auxin influx carrier (AUX/LAX)

The cellular movement of auxin is facilitated by the combined activities of the auxin influx and efflux carriers. The existence of auxin influx carrier came from the reports of Rubery and Sheldrake in 1974 (Rubery and Sheldrake 1974) where saturable auxin uptake in crown gall suspension cells of *Parthenocissus tricuspidata* was observed. Further, evidence about the presence of auxin transporters came when uptake of Indole-3-acetic acid (IAA) by sealed zucchini membrane vesicles was noticed and this was seen as an active process driven by the proton motive forces with the help of an auxin influx carrier, which was expected to be a proton symporter (Lomax et al. 1985). This hypothesis was later supported by Sabater and Rubery (1987). It has been seen that AUX/LAX auxin transporter homologs are present throughout the plant kingdom and they may have evolved before the evolution of the land plants as AUX/LAX-like sequences were also reported in several unicellular and colony forming Chlorophyta as well (De Smet et al. 2011; Swarup and Péret 2012).

3.1. Genomics, structure, polarity, and localization of AUX/LAX

The *AUX1* gene belongs to a small gene family and consists of four members in *Arabidopsis thaliana*, which includes *AUX1* and like-AUX1 (LAX) (*LAX1*, *LAX2*, and *LAX3*). These are plant-specific proteins within the amino acid/auxin permease super-family (Young et al. 1999; Peret et al. 2012). The genome of *Oryza sativa* (rice) encodes for five AUX/LAX transporter in comparison to three *AUX1/LAX* transporters in *A. thaliana* (Chai and Subudhi 2016). AUX/LAX proteins harbor membrane-spanning transmembrane domains and present in the plasma membrane as well as in sub-cellular compartments (Figure 1, Table 1, Fig. S1). The AUX/LAX proteins present in the plasma membrane have nine (OsLAX5) and eleven (OsLAX3) transmembrane helices, respectively while as others (AtAUX1, AtLAX1, AtLAX2, AtLAX3, OsLAX1, OsLAX2, and OsLAX4) harbor ten transmembrane helices. The N-and C-terminal domains are present in the extracellular spaces whereas the transmembrane helices are embedded in the phospholipid bilayer. The AtAUX1 contains 485 amino acids out of which around 219 amino acids reside within the transmembrane helices. The AUX1/LAX proteins share a significant sequence similarity and also contain conserved motifs (Fig. S2). A few of the conserved motifs of AUX/LAX proteins are W-H-G-G-S-x_2-D-A-W-F-S–C-A-S-N-Q-V-A-Q-V-L-L-T-L-P-Y-S-F, Q-L-G-M-x-S-G-I, F-Y-G-x-L-G-S-W-T-A-Y-L-I-S-V-L-Y-x-E-Y-R, N-H-V-I-Q-W-F-E-V-L-D-G-L-L-G, G-L-x-F-N–C-T-F-L-L-F-G-x-V-I-Q-L-I-x-C-A-S-N-I-Y-Y-I-N-D, D-K-R-T-W-T-Y-I-F-G-A-C–C-A-T-T-V-F-I-P-S-F-H-N-Y-R-I-W-S-F-L-G-L-x-M-T-T-Y-T-A-W-Y, Y-F-T-G-A-T-N-I-L-Y-T-F-G-G-H-A-V-T-V-E-I-M-H-Y-A-M-W, T-L-T-x-P-S-A, Y-W-A-F-G-D-x-L-L-x-H-S-N-A-x_2-L-L-P, R-D-x-A-V-I/V-L-M-L-I/V-H-Q-F-I-T-F-G-F-A-C-T-P-L-Y-F-V-W-E-K, and R-L-P-V/I-V-x-P-I-W-F-x-A-I-I-F-P-F-F-G-P-

Table 1. Sub-cellular localization of auxin transporter proteins in plants.

Protein	Protein domain	Sub-cellular localization
AUX/LAX		
AtAUX/LAX	Integral membrane protein	Plasma membrane
AtLAX1	Integral membrane protein	Plasma membrane
AtLAX2	Integral membrane protein	Plasma membrane
AtLAX3	Integral membrane protein	Plasma membrane
PIN		
AtPIN1	Integral membrane protein	Plasma membrane
AtPIN2	Integral membrane protein	Plasma membrane
AtPIN3	Integral membrane protein	Plasma membrane
AtPIN4	Integral membrane protein	Plasma membrane
AtPIN5	Integral membrane protein	Endoplasmic reticulum
AtPIN6	Integral membrane protein	Plasma membrane
AtPIN7	Integral membrane protein	Plasma membrane
AtPIN8	Integral membrane protein	Plasma membrane
ABCB		
AtABCB1	Integral membrane protein	Plasma membrane
AtABCB2	Integral membrane protein	Mitochondrial
AtABCB3	Integral membrane protein	Plasma membrane
AtABCB4	Integral membrane protein	Plasma membrane
AtABCB5	Integral membrane protein	Plasma membrane
AtABCB6	Integral membrane protein	Plasma membrane
AtABCB7	Integral membrane protein	Plasma membrane
AtABCB9	Integral membrane protein	Plasma membrane
AtABCB10	Integral membrane protein	Plasma membrane
AtABCB11	Integral membrane protein	Plasma membrane
AtABCB12	Integral membrane protein	Plasma membrane
AtABCB13	Integral membrane protein	Plasma membrane
AtABCB14	Integral membrane protein	Plasma membrane
AtABCB15	Integral membrane protein	Plasma membrane
AtABCB16	Integral membrane protein	Plasma membrane
AtABCB17	Integral membrane protein	Plasma membrane
AtABCB18	Integral membrane protein	Plasma membrane
AtABCB19	Integral membrane protein	Plasma membrane
AtABCB20	Integral membrane protein	Plasma membrane
AtABCB21	Integral membrane protein	Plasma membrane
AtABCB22	Integral membrane protein	Plasma membrane
PILS		
AtPILS1	Integral membrane protein	Endoplasmic reticulum
AtPILS2	Integral membrane protein	Endoplasmic reticulum
AtPILS3	Integral membrane protein	Endoplasmic reticulum
AtPILS4	Integral membrane protein	Not detected
AtPILS5	Integral membrane protein	Endoplasmic reticulum
AtPILS6	Integral membrane protein	Endoplasmic reticulum
AtPILS7	Integral membrane protein	Endoplasmic reticulum
OsPILS1	Integral membrane protein	Vacuole
OsPILS2	Integral membrane protein	Endoplasmic reticulum
OsPILS5	Integral membrane protein	Endoplasmic reticulum
OsPILS6a	Integral membrane protein	Vacuole
OsPILS6b	Integral membrane protein	Endoplasmic reticulum
OsPILS7a	Integral membrane protein	Endoplasmic reticulum
OsPILS7b	Integral membrane protein	Plasma membrane & Endoplasmic reticulum

I-N-S-x-V-G-x-L-L-V-F-T-V-Y-I-I-P-x-L-A-H (Fig. S2). The presence of conserved motifs in AUX/LAX signifies their conserved roles in auxin signaling events. The details regarding the functionalities of these conserved motifs are provided in the supplementary file (Table S1).

The localization of AUX1 is either non-polar or polar, which depends on the cell or the tissue types. For instant, it is present in the apical position in protophloem, whereas in the lateral root caps, it occupies the basal position. However, no such polarity patterns were seen in the columella cells (Bennett et al. 1996; Swarup et al. 2001). Besides this, *AUX1* also plays an important role in maintaining the cell polarity in root hairs. The AUX1 is not only present in the plasma membrane, but also in the sub-cellular compartments such as endosomes and the Golgi complex (Figure 1) (Kleine-Vehn et al. 2006). The plasma membrane localization of AUX1 requires endoplasmic reticulum (ER) chaperon, AUX_RESISTANT 4 (AXR4) (Dharmasiri et al. 2006). Auxin transport inhibitor disrupts the polar distribution of AUX1. Brefeldin A, a fungal toxin is the classic example of auxin response factor (ARF) inhibitor that inhibits the internal trafficking of AUX1 and leads to the disappearance of PIN proteins from the plasma membrane (Shevell et al. 1994; Kleine-Vehn et al. 2006). However, this process is fully reversible and it leads to constitutive cycling of PIN proteins between plasma membrane and endosomes (Geldner and Palme 2001).

3.2. Regulation and function of AUX/LAX

A few studies have demonstrated that organ-level signals are required for the regulation of AUX1-mediated auxin transport. For instance, Li et al. (2011) reported that shoots of *A. thaliana* that are supplied with ammonium cation inhibit the initiation of lateral roots (Li et al. 2011). This resulted due to the fact that *AUX1* is required for the formation of lateral root, and the shoot supplied with ammonium suppressed the expression of *AUX1* gene in the vascular tissue (Li et al. 2011). In contrast, application of *A. thaliana* shoots with iron triggers the initiation of lateral roots by inducing the expression

Table 2. Auxin transporter genes and their functions.

Genes	Functional role	References
AUX/LAX		
AtAUX1	Cell elongation, gametophyte development, embryogenesis, embryonic root cell organization	(Ugartechea-Chirino et al. 2010; Panoli et al. 2015; Robert et al. 2015; Street et al. 2016)
AtLAX1	Vascular pattern, xylem differentiation, gametophyte development, phylotaxis	(Bainbridge et al. 2008; Fàbregas et al. 2015; Panoli et al. 2015)
AtLAX2	Serration in leaf margin, vascular pattern in cotyledons, phylotaxis	(Bainbridge et al. 2008; Peret et al. 2012; Kasprzewska et al. 2015)
AtLAX3	Lateral root emergence, hook formation of hypocotyle, auxin homeostasis, phylotaxis	(Bainbridge et al. 2008; Swarup et al. 2008; Mellor et al. 2015; Porco et al. 2016; Yu et al. 2016)
PttLAX1-3	Development of vascular cambium	(Schrader et al. 2003)
PaLAX	Root gravitropism	(Hoyerová et al. 2008)
MtLAX1-5	Early nodule formation	(de Billy et al. 2001; Schnabel and Frugoli 2004)
MtLAX3	Plant growth, development, root and nodule development	(Revalska et al. 2015)
CsAUX1	Root gravitropism	(Kamada et al. 2003)
LaAUX1	Development of etiolated hypocotyl	(Oliveros-Valenzuela et al. 2007)
CgLAX1	Nodule formation	(Péret et al. 2007)
CgLAX3	Nodule formation	(Péret et al. 2007)
OsAUX1	Primary root and root hair elongation in Cd stress, lateral root initiation	(Yu et al., 2015, Zhao et al., 2015)
ZmAUX1	Root development	(Hochholdinger et al. 2000)
PINs		
AtPIN1	Embryogenesis, phyllotaxy, vein formation, development of lateral organ, & vascular development	(Müller et al. 1998; Benková et al. 2003; Reinhardt et al. 2003; Weijers et al. 2005; Scarpella et al. 2006)
AtPIN2	Root gravitropism, organogenesis	(Chen et al. 1998; Luschnig et al. 1998; Müller et al. 1998; Utsuno et al. 1998; Benková et al. 2003)
AtPIN3	Phototropism, gravitropism, and organ development	(Friml, Wiśniewska, et al. 2002b; Benková et al. 2003)
AtPIN4	Embryogenesis, root patterning	(Friml, Benková, et al. 2002a; Benková et al. 2003; Friml et al. 2003; Weijers et al. 2005; Dhonukshe et al. 2007)
AtPIN5	Intracellular auxin homeostasis	(Mravec et al. 2009)
AtPIN6	Auxin transport activity	(Benková et al. 2003; Petrášek et al. 2006)
AtPIN7	Root development, embryogenesis	(Benková et al. 2003; Friml et al. 2003)
MdPIN1	Inhibition of primary root, increased lateral root, enhanced phototropism and geotropism	(An et al. 2016)
NtPIN4	Axillary bud growth	(Xie et al. 2017)
OsPIN1	Adventitious root emergence & tillering, shorter plant height	(Xu et al. 2005; Chen et al. 2012)
ABCBs		
AtABCB1, AtABCB19	Dwarfism	(Noh et al. 2001)
AtABCB4	Root hair development	(Cho et al. 2007)
AtABCB14	Vascular development	(Kaneda et al. 2011)
AtABCB19	Root gravitropism, post embryonic organ separation	(Zhao et al. 2013; Cho et al. 2014)
OsABCB14	Iron homeostasis	(Xu et al. 2014)
PILS		
AtPILS1	Ectopic expression line shows dwarf and or bushy plant, defect in flower development, sterility in T1 generation, homeotic transformation of flower organ to flower buds, triplication of gynoecium, unfused carpel, enhanced hypocotyls growth, higher lateral root	(Barbez et al. 2012)
AtPILS2	Lateral root development	(Barbez et al. 2012)
AtPILS3	Ectopic expression line shows dwarf and or bushy plant, defect in flower development, sterility in T1 generation, homeotic transformation of flower organ to flower buds, triplication of gynoecium, unfused carpel. Reduced root hair length	(Barbez et al. 2012)
AtPILS5	Reduced hypocotyls growth, gravitropism, hyposensitive root growth	(Barbez et al. 2012)

of *AUX1* gene (Giehl et al. 2012). AUX1 is required for long-distance auxin transport, from the shoot tip in a basipetal fashion towards the roots, through vascular bundle whereas LAX is involved in the maintenance of the local auxin gradients (Swarup et al. 2002; Swarup et al. 2004; Swarup et al. 2008).

The AUX/LAX encodes a putative auxin carrier domain and a mutation in these proteins manifests in auxin-related developmental defects (Table 2) (Bennett et al. 1996; Swarup et al. 2004; Swarup et al. 2008). Characterization of *aux1* mutant revealed that they are sensitive towards the application of different auxins, however root gravitropic defect of *aux1* can be rescued only by the application of 1-naphthalene acetic acid (1-NAA) (Yamamoto and Yamamoto 1998; Marchant et al. 1999). It has been seen that *aux1* mutants are defective in the basipetal auxin transport and *AUX1* is expressed in columella, epidermis, and in the pericycle, ahead of the first periclinal division (Swarup et al. 2001). The direct experimental evidence of AUX1 function as an auxin permease came from the study of Yang et al. (2006) where they provided a direct empirical evidence for auxin permease function of AUX1 where they expressed *AUX1* in *Xenopus laevis* oocyte and found a pH dependent increase in IAA uptake (Yang et al. 2006). Later Carrier et al. (2008) demonstrated the binding affinity of the IAA with AUX in a pH-dependent manner where maximum binding was seen between pH 5 and 6 (Carrier et al. 2008). This may also explain the reason for the localization of AUX/LAX in the endo-membrane of the sub-cellular compartments, as pH in endosomes ranges from 4.5 to 6.5. Therefore, these proteins may have evolved due to non-redundant expression and became sub-fractionalized in order to participate in auxin-related developmental processes in different tissues and organs. The AUX/LAX is involved in regulating lateral root development (De Smet et al. 2007; Swarup et al. 2008). The *aux1* mutant of *A. thaliana* produced 50% fewer lateral roots than the control (Hobbie and Estelle 1995). It is interesting to note that although *AUX1* is very crucial for the development of root hair, its expression is only seen in the neighboring cells but not in the root hairs (Jones et al.

2009). Although, the expression of *AUX1* was not seen in the root hair cells, still *aux1* mutant had relatively short root hairs. This abnormal phenotype of *aux1* mutant later restores to the wild type upon application of exogenous auxin. Therefore, it clearly demonstrates its role in root hair development (Jones et al. 2009). In the mutant of *werewolf/myb23*-that lacked non-hair cells, expression of *AUX1* was not detected in the epidermis. These mutants had shorter root hairs that could be restored to the wild-type by auxin treatment. Therefore, it is clear that the non-hair cells, have a direct impact on the development of root hairs and also affect the auxin concentration in root hair cells (Jones et al. 2009). In a simulation study it was found that, expression of *AUX1* in non-hair cells increases the auxin concentration by more than ten times compared to the adjacent hair cells, suggesting the role of *AUX1* in regulation of high auxin balance between non-hair and hair cells to facilitates the growth and development of roots (Jones et al. 2009; Swarup and Péret 2012).

Except *AUX1*, no other members of the *AUX/LAX* family participate in the root gravitropic responses (Peret et al. 2012). *LAX2* and *LAX3* are only expressed in columella cells. The *lax2* and *lax3* single mutant do not exhibit any root gravitropic defects and *lax2 aux1* double mutant does not show any defects that are sever than *aux1* single mutants (Peret et al. 2012). However, *LAX3* plays a significant role in the regulation of lateral root development (Swarup et al. 2008). The *lax3* mutant has a reduced number of lateral roots. Swarup et al. (2008) reported that, *LAX3* is expressed in the epidermis and cortical cells, most specifically, in front of the lateral root primordia (Table 2) (Swarup et al. 2008). Earlier Benková et al. (2003) reported that auxin maxima is located in the lateral root primordia and hence it is possible that *LAX3* expression can have a significant impact in formation of auxin maxima (Benková et al. 2003). Besides this, several cell wall remodeling genes are also co-expressed with *LAX3* (Swarup et al. 2008). Auxin from the lateral root primordia enters the cortical cells and induces the expression of the *LAX3* gene. LAX3 protein in the plasma membrane facilitates auxin uptake and reinforces its expression within the same cell. Consequently, a higher level of auxin accumulates in the cortical cells, which ultimately induces the expression of cell wall remodeling enzymes. Proteins of these family members are targeted towards the plasma membrane, however, LAX2 and LAX3 failed in getting localized to the plasma membrane that express AUX1 in tissues (Peret et al. 2012). This suggests that there are some molecular factors present in the auxin influx carrier or there might be some cell tissue-specific regulators that are operational during the intracellular trafficking of different members of the AUX/LAX family. Peret et al. (2012) suggested that there might be specific molecular chaperones that are required for the regulation and trafficking of specific AUX/LAX proteins (Dharmasiri et al. 2006; Peret et al. 2012).

4. Auxin efflux carrier (PIN)

4.1. Genomics, structure, polarity, and localization of PINs

The auxin efflux carrier (PIN) is an important protein that coordinates and channels auxin transport. Upon influx of auxin by AUX/LAX, it is highly important to efflux it out so as it reaches the next cell and this is where the role of the auxin efflux carrier becomes important. The auxin efflux carrier is found in almost all land plants, including bryophytes, Lycopodiopsidae, monocot and eudicots (Křeček et al. 2009; Mohanta and Mohanta 2013; Singh et al. 2015). In *A. thaliana*, there are eight members of the PIN gene family that divided into four sub-groups while the crop plant *O. sativa* encodes 12 *PIN* genes in its genome (Křeček et al. 2009; Wang et al. 2009). The *A. thaliana* PIN sub-groups are PIN1 and 2; PIN3, 4 and 7; PIN6; and PIN5 and 8. In *O. sativa* the *PIN* genes are named as *OsPIN1a-d, OsPIN2, OsPIN5a-c, OsPIN8, OsPIN9* and *OsPIN10a-b* (Wang et al. 2009). In terms of evolutionary plant lineage, *PIN* genes are grouped into seven groups (Křeček et al. 2009). Their diverse molecular phylogeny reflects their functional diversification within the *PIN* sub-groups during the evolution. The length of the PIN protein sequences ranges from 351 to 647 amino acid residues. The exon-intron position of *A. thaliana PINs shows AtPIN1, AtPIN4* and *AtPIN7* are close to each other. Unlike *AtPIN1*, *AtPIN1* shares much closer relation with *AtPIN3, AtPIN4*, and *AtPIN7*. Although, genetic architecture of the *AtPIN1* gene correlates more with the *AtPIN3, AtPIN4*, and *AtPIN7* than with *AtPIN2,* but still, it is sub-grouped with AtPIN2 at the protein level. This suggests that the structural conservation at protein level is more important than the sequence conservation at the genomic level. The homology for *A. thaliana PIN* genes has been identified in most of the land plants and the numbers of *PIN* genes vary greatly among different species.

PIN proteins are membrane bound and have five to ten membrane-spanning transmembrane helices. The number of transmembrane helices present in different PIN proteins are as follows; five in OsPIN8 and OsPIN10a, seven in OsPIN5a, OsPIN5b and OsPIN5c, eight in AtPIN8, nine in AtPIN1, AtPIN2, AtPIN3, AtPIN5, AtPIN6, AtPIN7, OsPIN1c, and OsPIN2 and ten in AtPIN4, OsPIN1a, OsPIN1b, OsPIN9 and OsPIN10b. The N- and C-terminal domains of the PIN protein are connected by a central hydrophilic loop. Depending upon the length of this hydrophilic loop, PIN proteins are classified as a short or long-domain PIN protein. The PIN protein whose hydrophilic loop contains more than 50 amino acids is refereed as a long domain PIN protein, whereas those having less than 50 amino acid residues are refereed as a short domain PIN proteins. PIN1-4, PIN6 and PIN7 and their close orthologs have a long hydrophilic loop whereas PIN5, PIN8 and their close orthologs have a short hydrophilic loop. Multiple sequence alignment shows the presence of several conserved motifs in the N-and C-terminal region as well as in the dynamic hydrophilic region. The long PINs possess conserved P-L-Y-x-A, D-Q-C–S-G-I-N-R, A-V-P-x-L-x-F, A-A-D-x-L-x-K, L-D-x_2-I-T-x-F-S-x_3-L-P-N-T, V-M-G-I-P-L-L-x-M-Y, L-M-x-Q-x-V-V-L-Q, I/V-W-Y-x_4-F-L-F-E, Q-F-P, V-D-x-D-V-x-S-L, P-R-x-S-N-L-x_3-E-I-Y-S and T-P-R motifs in the N-terminal end (Fig. S3). In C-terminal domain they possess conserved P-V-x-D, P-x-S-V-M-x-R-L-I-L, V-x-R-K-L-x-R-N-P-N-T-Y-x-S-L-x-G, M-P-x-I-x_3-S, L-G-M-x-M-F-S-x-G-x-F-x-A-x-Q, A-I-V-Q-A-A-L-P, F-V-F-x_2-E-Y, L-S-T-x-V-I, and L-P-I-T-x-Y-Y-I-x-L-G motifs (Fig. S3). The short PINs have conserved P-L-Y, E-Q-C-x_2-V/I-N, and N/D-P-F/Y motifs at the N-terminal end and G-x_2-W-A, G-x-G-x_2-M-F, A-I-x-Q-A, A-L-P-Q, F-I/V-F-A-K-E-Y, and S-T-V-I motifs at the C-terminal end (Fig. S4). Previous studies have also reported the presence of conserved motifs in PIN proteins (Mohanta et al. 2014;

Mohanta and Bae 2017). The long PINs are localized to the plasma membrane in a polarized fashion, whereas the short PINs are predominantly localized in the sub-cellular compartments like endoplasmic reticulum (ER) (Figure 1) (Křeček et al. 2009; Mravec et al. 2009; Ganguly et al. 2010; Bosco et al. 2012; Ding et al. 2012). The long PINs are localized asymmetrically in the plasma membrane for directional flow of auxin and to create auxin gradients (Figure 1). PIN5 protein is consistently localized to ER whereas PIN8 has a dynamic localization and can be found in ER as well as in the plasma membrane (Ganguly et al. 2010). This dynamic nature of the short hydrophilic loop involved in the localization of PIN8 to the plasma membrane varies with the cell type (Ganguly et al. 2010). Molecular cues in the short hydrophilic loop of PIN protein could be the possible reason for this. Similarly, the long hydrophilic loop might also have diverse molecular signatures for trafficking of PIN proteins to the plasma membrane, clathrin-mediated endocytosis, and also in various phosphorylation, and ubiquitylation events (Grunewald and Friml 2010; Kleine-Vehn et al. 2011; Ganguly et al. 2012; Leitner et al. 2012).

PIN1, PIN3, PIN4, and PIN7 are localized to the basal side of the cell facilitating basipetal auxin flow towards the root cells (Friml, Benková, et al. 2002a; Friml, Wiśniewska, et al. 2002b; Blilou et al. 2005). Localization of PIN1 in the plasma membrane of the leaf primordia which arise from the shoot apical meristem establishes auxin maxima for the inception of developmental events in leaf (Reinhardt et al. 2003). Apical localization of PIN2 in root epidermal cells promotes auxin transport from the root tip acropetally towards the upper end (Luschnig et al. 1998; Muller 1998). Basal localization of PIN2 in the root cortex along with the lateral localization of PIN3 in the pericycle directs auxin flow back to the root meristem (Blilou et al. 2005). In the root columella, PIN3 and PIN7 are redistributed due to the gravity vector which causes gravitropic bending of roots in the plants (Friml, Wiśniewska, et al. 2002b; Kleine-Vehn et al. 2010). During phototropism, the activity of PIN3 decreases on the illuminated side of the hypocotyl to facilitate auxin transport to the non-illuminating side (Ding et al. 2011).

4.2. Regulation and function of PINs

The study of tissue-specific expression of *O. sativa PIN* genes revealed that *OsPIN* genes were constitutively expressed in stems, leaves and young panicles (Wang et al. 2009). *OsPIN1a* and *OsPIN1b* were highly expressed in the aforementioned tissues, while low expression of *OsPIN1c* was seen in young panicles and leaves. The *OsPIN2* has weak expression in stem, leaves, and young panicles whereas expression of *OsPIN5a* was higher than *OsPIN5b* in young panicles (Wang et al. 2009). Higher expression of *OsPIN9* was seen in the base of the stem and root than other tissues. *OsPIN10a* was highly expressed in all tissues except the roots whereas, *OsPIN10b* was relatively highly expressed in the leaves (Wang et al. 2009). A GUS driven assay revealed, *OsPIN1a* was expressed in root cap whereas, *OsPIN1b, OsPIN1c* and *OsPIN9* were predominantly expressed in the stele. *OsPIN1b, OsPIN1c, OspIN5a* and *OsPIN5b* were detected in the meristems. *OsPIN1c* exclusively expressed in the root primordia (Wang et al. 2009). *OsPIN1a, OsPIN1c* and *OsPIN10b* were expressed in flower veins of hull and anthers whereas, *OsPIN1a* had high expression in root primordia and the vascular tissue (Wang et al. 2009). The expression of *OsPIN* genes was also modulated in *O. sativa* in the presence of exogenous auxin and cytokinin (Singh et al. 2015). The expression pattern of *OsPIN5c* is very negligible in auxin and cytokinin treated root tissues. Significant transcript accumulation of *OsPIN1b, OsPIN2* and *OsPIN9* occurs in auxin and cytokinin treated *O. sativa*. In 7 days old seedlings treated with auxin, the expression of *OsPIN2* is up-regulated by four folds. *OsPIN1b* and *OsPIN9* were significantly up-regulated in 7 days rice seedling upon treatment with cytokinin while auxin treatment up-regulates their expression at 14 and 21 days time period (Singh et al. 2015). Firml et al. (2003) reported the expression of *PIN* genes during the embryogenesis of *A. thaliana* (Friml et al. 2003). *AtPIN1* and *AtPIN3* expressed in apical and columella cells, respectively (Friml et al. 2003). The localization of AtPIN4 protein was detected in the hypophysis and provascular initials of root meristem. The expression pattern of *AtPIN7* resembled to that of *AtPIN1* (Friml et al. 2003). To understand the correlation between the AtPIN1 and AtPIN7 during early embryogenesis, detection of AtPIN1 protein was seen from one to sixteen-cell stage, in all newly formed cell boundaries. No polarity patterns were seen at this stage, but polarity of AtPIN1 was detected at thirty two cell stage. It was localized to provascular cells facing towards the basal embryo pole. AtPIN1 later shifted to the quiescent center cells on the basal side. AtPIN7 was present in the apical and basal cells during the post-zygotic division in the endomembrane (Friml et al. 2003). AtPIN7 was found in the apical position of the suspensor cell at thirty-two cell stage thus making it as a polarity marker and later its position shifted to the basal side of the suspensor cell post 32-cell stage, followed by its appearance in the boundary wall. This concluded that the accumulation of AtPIN1 in the proembryo cells and shifting/reversal of AtPIN7 polarity are directly correlated with the apical-to-basal reversal of auxin gradient (Jirí Friml et al. 2003). Besides this, analysis of *pin7* mutant revealed its participation in auxin distribution and the embryos with *pin7* mutation failed to establish the apical-basal auxin gradient (Jirí Friml et al. 2003). Mutational analysis revealed that *PIN1* and *PIN4* are involved in organogenesis; *PIN2* and *PIN3* participate in root gravitropism; *PIN1* and *PIN3* actively participate in phototropism and *PIN1, PIN3, PIN4* and *PIN7* are involved in embryogenesis (Table 2) (Paponov et al. 2005). *A. thaliana pin1* mutant (PIN-FORMED) lacks an organ in the inflorescence which results in its deformed structure (Okada et al. 1991). Similarly, loss of *PIN2* leads to defects in root gravitropism and growth of root hairs, suggesting their crucial role in diverse developmental process (Chen et al. 1998; Luschnig et al. 1998; Muller 1998; Utsuno et al. 1998).

5. ATP-binding cassette transporters (ABCB)

5.1. Genomics, structure, polarity, and localization of ABCBs

The POLYGLYCOPROTEIN (PGP) / MULTIDRUG RESISTANCE (MDR)/ATP-binding cassette transporters of B class (ABCB) proteins belong to the super family of ABCB transporters and most of the plant ABCB proteins characterized have been found to be auxin transporters (Noh et al. 2001; Luschnig 2002; Terasaka et al. 2005; Geisler and Murphy 2006). There are twenty one known ABCB members out of which ABCB1, ABCB4 and ABCB19 are

involved in auxin transport (Table 2) (Noh et al. 2001; Multani et al. 2003; Geisler et al. 2005; Terasaka et al. 2005; Geisler and Murphy 2006; Cho et al. 2007). However, a recent report revealed that ABCB14 and ABCB15 also participate in polar auxin transport (Kaneda et al. 2011). Another study suggests that ABCB1, ABCB4 and ABCB19 have lower auxin exporting capacities compared to their counterpart PIN proteins (Cho and Cho 2013). The model plant *A. thaliana* has twenty one ABCB proteins whereas *O. sativa* has twenty-two, *Sorghum bicolor* has twenty-four and *Zea mays* has thirty-five (Chai and Subudhi 2016). All auxin-transporting PIN proteins have been found in the same clade during the phylogenetic analysis, whereas ABCBs fall into three distinct clades (Cho and Cho 2013). The *O. sativa* OsABCBs contain proteins ranging from 524 (OsABCB17) to 1482 (OsABCB12) amino acids. The molecular weights of OsABCB varies from 56 (OsABCB17) to 158 (OsABCB12) kDa and the isoelectric point ranges from 5.7 (OsOsABCB21) to 9.3 (OsABCB11) (Chai and Subudhi 2016). The diverse molecular weights and isoelectric points of ABCB proteins allow them to participate in polar movement across the cell. Besides this, such diverse molecular properties of ABCBs might allow them to interact with cell polarity complex to complete their function. ABCB localize to the plasma membrane and are dynamically distributed there, this might be due to their dynamic molecular weights, and isoelectric points (Figure 1). Except OsABCB8 and OsABCB22, the majority of the OsABCBs are predicted to be localizing to the plasma membrane (Chai and Subudhi 2016). OsABCB12 and OsABCB17 localize to the chloroplast. The OsABCBs have 4-13 membrane-spanning transmembrane helices and based on their topological character of transmembrane domain, they are divided into two groups (Chai and Subudhi 2016). Most OsABCBs have two transmembrane helices at the N- and C-terminal ends and are linked by a central loop of variable length whereas OsABCB10, OsABCB16 and OsABCB17 have one cluster transmembrane helices (Chai and Subudhi 2016). The transmembrane helices of N- and C-termini are conserved and the loops are highly variable (Chai and Subudhi 2016). The transmembrane domain of the ABCB transporter has a nucleotide binding domain as well (Geisler and Murphy 2006). The ABCB19 is confined to the detergent-resistant membrane (DRM) region of the plasma membrane where glucosyl-ceramide and sitosterol are abundant (Titapiwatanakun et al. 2009). ABCB19 defines the membrane structure and provides a platform for the stable localization of PIN1 (Titapiwatanakun et al. 2009). Multiple sequence alignment shows the presence of conserved motifs in ABCB proteins. The major conserved motifs present at the N-terminal end of ABCB proteins were, A-x-V-G-x_2-G-x-G-K-S, E-R-F-Y-D-P, V-x-Q-E-P-x-L, I-x-E-N, V/I-G-E-x-G-x_2-L-S-G-G-Q-K-Q-R-I-x-I-A-R-A, P-x-I-L-L-L-D-E-A-T-S-A-L-D-x-E-S-E-x_2-V-Q-D-A-L-D, R-T-T-x-V/I-V/I-A-H-R-L-x-T-I/V, and G-x_3-E-x-G-x-H-x-E-L. The conserved motifs present at the C-terminal ends were E-x_2-W-F-D, V-G-x-S-x_2-G-K-S, R-F-Y-D, V-x-Q-E-P, G-Y-x-T-x-G-x_2-G-x-Q-L, G-Q-x-Q-R-I-A-x-A-R, I-x-L-x-D-E-A-x-S-x_2-D and T-x-V/I-V/I-A-H (Fig. S5). The G-x_2-G-x-G-K-S domain of conserved A-x-V-G-x_2-G-x-G-K-S region is known as Walker A motif and L-S-G-G-Q of conserved V/I-G-E-x-G-x_2-L-S-G-G-Q-K-Q-R-I-x-I-A-R-A motif is known as Walker B motif (Holland and Blight 1999; Orelle et al. 2003). The underlined Q-K-Q-R-I-x-I-A-R-A, I-L-L-L-D-E-A-T-S-A-L-D and G-Q-x-Q-R-I-A-x-A-R motifs are the characteristic conserved sequences of ABC transporter family (Guillemette et al. 2004). These two motifs are the characteristic features of the ABC-ATPase protein and they collectively constitute the nucleotide binding motif. These conserved motifs might play a crucial role in transporting of auxin molecules across the plasma membrane. In animals, mutation in ABCB protein leads to several serious genetic diseases and over expression leads to multi-drug resistance in bacteria, viruses and cancer (Stolarczyk et al. 2011). The P-glycoprotein ABCB proteins contain a linker region having consensus phosphorylation site, suggesting its functional regulatory role (Davies and Coleman 2000). The ABC transporter gets their energy from breakdown of ATP and act like ATPases as well. Study led by Aryal et al. (2015) described that ABC transporters are regulated through protein phosphorylation event (Aryal et al. 2015). In addition to the role of auxin transport, ABC transporter protein AtABCG25 involved is in abscisic acid transport as well (Kuromori et al. 2010).

5.2. Regulation and function of ABCBs

The ABC super-family consists of many universal transporters associated with the movement and transport of various small molecules, nutrients and xenobiotics. A comparative study between the bacterial and murine ABC transporter with the plant ABCB transporter revealed an exceptionally high degree of structural conservation. Although a remarkable structural conservation was found between them, the ABCBs exhibits limited substrate specificity in certain organisms but are promiscuous in others. In some cells, ABCB shows polarity while in others they do not (Geisler et al. 2005; Terasaka et al. 2005; Blakeslee et al. 2007; Cho et al. 2007; Wu et al. 2007; Mravec et al. 2008; Cho et al. 2012). Unlike PIN and AUX/LAX, the ABCB proteins serve as either facultative auxin influx/efflux carrier (ABCB21) or auxin carrier with fixed direction (ABCB1, ABCB4 and ABCB19) (Table 2) (Geisler and Murphy 2006; Cho et al. 2012; Kamimoto et al. 2012). The facultative or directional auxin flow by ABCBs depends on the cellular auxin level (Geisler and Murphy 2006; Cho et al. 2012; Kamimoto et al. 2012). ABCB is predominantly non-polar and could determine the amount of auxin concentration available for PIN mediated polar auxin transport (Mravec et al. 2008).

Although auxin transport is required for both short and long-distance delivery of auxin, the long distance transport from the shoot tip to the root is conducted by ABCB1 and ABCB19 along with PIN1 and PIN7 (Gälweiler 1998; Friml et al. 2003; Blakeslee et al. 2007). The polarity of ABCB localization might be associated with the secondary cell wall and early stages of cytokinesis rather than the cell plate formation (Blakeslee et al. 2007; Titapiwatanakun et al. 2009). The expressions of *ABCB1* and *PIN7* are predominantly restricted to the shoot apex and both are persistent in their act during auxin loading to the vascular stream (Zažímalová et al. 2010). The expression of *ABCB19* and *PIN1* occurs throughout the plant and they maintain the auxin flow from the shoot apex to the root apex (Zažímalová et al. 2010). Acropetal auxin flow from the base of the root to the root tip is directed by ABCB1 and PIN. Auxin gets distributed to the epidermal cells (basipetal flow) and lateral root cap by the action of ABCB1, ABCB4, ABCB19, AUX1, PIN1, PIN2, PIN3, and

PIN4. Along with other auxin transporters, ABCB1 and ABCB19 function in loading, while ABCB1, and ABCB4 along with PIN2 continue the auxin stream along the epidermal cells, cortical cells, and root cap to drive the cell division, cell elongation and root hair development (Gälweiler 1998; Muller 1998; Swarup et al. 2001; Friml, Benková, et al. 2002a; Geisler et al. 2005; Terasaka et al. 2005; Blakeslee et al. 2007; Mravec et al. 2008). Although ABCB19 and PIN1 are the principal mediators of polar auxin transport along the axis (Gälweiler 1998; Blakeslee et al. 2007), the retention of auxin in the stream of vascular transport is mediated by the combined activities of ABCB19 and PIN3 which localized to the bundle sheath cells (Friml et al. 2002b, Blakeslee et al. 2007). The ABCB19 that localizes in the endodermis and pericycle might have similar functions in the root (Blakeslee et al. 2007). The long-distance auxin flow, upwards from the root apex in the epidermal cells above the elongation zone is mediated by ABCB transporters (Geisler et al. 2005; Terasaka et al. 2005; Lewis et al. 2007; Titapiwatanakun et al. 2009; Zažímalová et al. 2010). ABCB4 regulates auxin homeostasis in root trichoblasts (Cho et al. 2007; Yang and Murphy 2009). The ABCB4 has import activity at low auxin concentrations. As the level of auxin increases, its function is reversed and changes to export activity (Yang and Murphy 2009). Hence the function of ABCB4 is to maintain auxin homeostasis when AUX1 is not present and it is confined to regions such as root hair and elongating cell zones where auxin levels are usually stable.

Besides auxin transport, ABCB proteins also participate in other diverse functions. OsABCB14 functions in both auxin transport and iron homeostasis (Xu et al. 2014). Other ABCBs are involved in calcium homeostasis, aluminum detoxification, stomatal response to CO_2 and secondary metabolite transport (Sasaki et al. 2002; Shitan et al. 2003; Lee et al. 2008). Several studies reported about the role of direct interaction between AtABCB and PIN towards the coordinated polar auxin transport (Bandyopadhyay et al. 2007; Blakeslee et al. 2007). Interactions of ABCB with PIN are vital for embryogenesis and organogenesis (Mravec et al. 2008). The *abcb* mutants have a defective cell elongation and long-distance transport of auxin. However, only limited defect is present in embryo development and organogenesis (Noh et al. 2001; Geisler et al. 2003; Terasaka et al. 2005; Blakeslee et al. 2007). Lee et al. (2008) reported that ABCB14 is a malate transporter and competitive transport occurs in conjunction with auxin as well (Lee et al. 2008). The *abcb14* mutants exhibit reduced malate-inhibitable auxin transport in the shoot (Zažímalová et al. 2010).

A protein known as TWISTED DWARF1 (TWD1) directly interacts with ABCB1 and ABCB19. The phenotype of *twd1* loss-of-function mutant is similar to the *abcb1/abcb19* mutants (Murphy et al. 2002; Geisler et al. 2003). This shows that, TWD1 is an activator of membrane localized ABCB complexes and alters conformational changes of ABCB proteins (Geisler et al. 2003; Bouchard et al. 2006; Bailly et al. 2008). The localization of ABCB1, ABCB4 and ABCB19 in the plasma membrane was severely compromised in *twd1* mutant (Wu et al. 2010). TWD1 protein is localized to the plasma membrane and endoplasmic reticulum. This suggests that ER-localized TWD1 protein serve for trafficking of ABCB protein and plasma membrane bound TWD1 modulate the activity of ABCB protein. TWD1 protein directly binds to the PINOID (PID) and TWD1-PID interactions regulate ABCB1-mediated auxin transport (Henrichs et al. 2012). In the absence of PWD1, PID phosphorylates the serine residue at position 634 in the ABCB linker domain and increases ABCB1-mediated auxin signaling (Henrichs et al. 2012). When the serine amino acid at position 634 is replaced by alanine (A), it leads to a defect in phosphorylation and when substituted by glutamate (E), it results in mimicking the phosphorylation. The substitution by A leads in reduced auxin export activities whereas substitution by E enhances auxin export activities (Henrichs et al. 2012). It has been reported that, ABCB19 is the substrate of PHOT1, and PHOT1-dependent phosphorylation of ABCB19 inhibits auxin-efflux activity, which triggers production of higher auxin levels above the hypocotyl apex (Christie et al. 2011). Later these auxin is channeled by PIN3 to the shoot elongation zone (Christie et al. 2011). Furthermore, the endogenous plant flavonoids that emerged in the early land plants obstruct with the principal mechanism of ABCB transporters while PIN proteins are indirectly affected by flavonoids (Rausher 2006; Peer and Murphy 2007; Santelia et al. 2008). This suggests that plant flavonoids might have a selective force in the evolution of plasma membrane mediated auxin efflux. The *mdr1* mutant exhibits epinasty of the cotyledons and the first true leaves (Noh et al. 2001). Besides this, it also produced waviness in the hypocotyls and roots (Noh et al. 2001). Defects in *ABCB4* produces longer root hairs than the wild type, whereas *abcb14* mutant produces slightly altered vascular development in the florescence stem (Noh et al. 2001; Cho et al. 2007). The *abcb1 abcb19* double mutant shows dwarfism in *A. thaliana* (Noh et al. 2001). The *abcb19* and *abcb1 abcb19* mutants display reduced root-directed auxin transport relative to *pin1*.

Recently, Chai et al. (2016) identified and analyzed the expression profiles of *ABCB* genes from *O. sativa* in response to phytohormone stimuli and abiotic stresses (Chai and Subudhi 2016). The authors reported twenty-two putative *OsABCB* genes from the rice genome. Most of the them were regulated by drought, salt and hormonal stimuli (Chai and Subudhi 2016). From twenty-two *OsABCB* genes, twenty-one were responsive to drought and salinity stress. Only *OsABCB22* was responsive to drought stress, but was unresponsive to the salinity stress. Most of the *OsABCB* genes were down regulated due to the salt/drought stresses, whereas only a few of them were up-regulated (*OsABCB5-7, OsABCB9-13, and OsABCB15-20*) in certain tissues. *OsABCB5, OsABCB12, OsABCB18*, and *OsABCB19* were up-regulated under drought and salinity stresses. In moderate drought conditions, the number of differentially expressed *OsABCB* genes in roots and leaves were seventeen and eighteen, respectively, whereas under severe drought stress, root expressed twenty-four *OsABCB* genes whereas leaves expressed only fifteen. Nevertheless, more genes were differentially expressed in roots than in leaves (fifteen vs. ten, respectively) (Chai and Subudhi 2016). The transcriptional regulation of *OsABCB* genes due to the drought and salinity stress indicates that they might be involved in the adaptation to abiotic stresses. Upon auxin treatment, twenty of the twenty-two *OsABCB* genes were expressed differently. Among them, four were exclusively expressed in the leaves, nine in the roots and ten in both leaves and roots (Chai and Subudhi 2016). Most of these auxin-regulated *OsABCB* genes were up-regulated and only four were down regulated at various time points. All *OsABCB* genes were modulated

due to abscisic acid (ABA) treatment. The modulation of *OsABCB* genes by auxin and abscisic acid treatments reflect their possible role in a hormonal cross talk, which enables plant to adapt various stress conditions.

6. PIN-likes (PILS)

6.1. Genomics, structure, polarity, and localization of PILS

Recently, a new family of auxin transporters have been reported known as PIN-likes (PILS) protein family (Barbez et al. 2012; Feraru et al. 2012; Mohanta et al. 2015). The topologies of PILS proteins are highly similar to the PIN proteins; hence they were named as PIN-likes (PILS) protein. Unlike PIN proteins, PILS also contain Interpro auxin carrier domain (Barbez et al. 2012; Feraru et al. 2012; Mohanta et al. 2015). *A. thaliana* and *O. sativa* contain seven *PILS* genes (Barbez et al. 2012; Mohanta et al. 2015). The PILS proteins in *A. thaliana* range in size from 390 (AtPILS3) to 472 (AtPILS1) amino acids (Feraru et al. 2012), whereas those in *O. sativa* range from 414 (OsPILS1) to 1280 (OsPILS5) amino acids (Mohanta et al. 2015). The molecular weight of OsPILS ranges from 44.076 (OsPILS1) to 140.721 (OsPILS5) kDa, whereas the isoelectric point lies between 6.91 (OsPILS5) to 8.38 (OsPILS1). The diverse range of molecular weight and isoelectric points of different PILS protein enables them to localize to different parts of the cell. *AtPILS3, AtPILS4,* and *AtPILS5* genes contain nine introns whereas *AtPILS1* contains eleven, *AtPILS6* contains eight and *AtPILS7* contains seven introns and *AtPILS2* is intronless. Similarly, from seven *OsPILS* genes, four (*OsPILS1, OsPILS6a, OsPILS6b*, and *OsPILS7a*) of them have ten introns, while *OsPILS5* has seven, *OsPILS7b* has nine and *OsPILS2* has only one intron. The orthologs of the *PILS2* gene either have one intron or it may be intronless. Phylogenetic analyses of OsPILS and AtPILS have revealed that the orthologs of *A. thaliana* AtPILS3 and AtPILS4 are absent in *O. sativa* (Mohanta et al. 2015).

Unlike PIN proteins, the PILS are also membrane bound proteins that are present inside as well as outside of the membrane of sub-cellular compartments (Figure 1, Table 2) (Mohanta et al. 2015). Except OsPILS5, all other PILS proteins contain ten transmembrane helices. In addition, OsPILS5 has only four transmembrane helices and the major part of the OsPILS5 is present outside of the membrane. The PILS proteins are characterized by the presence of two hydrophobic transmembrane domains at the N-and-C-terminal end (Feraru et al. 2012). The hydrophobic regions are organized into five transmembrane helices which are flanked by a short hydrophilic loop directed towards the cytosol (Feraru et al. 2012). Amino acid sequence analysis reveals the presence of a conserved N-x-G-N motif at the N-terminal end (Mohanta et al. 2015). The C-terminal of OsPILS has conserved A-P-L and G-G-N-L-G-x-x-G consensus sequences (Mohanta et al. 2015). The central hydrophilic loop is very dynamic and devoid of any conserved consensus sequence. Instead, it contains a conserved threonine amino acid in the hydrophilic loop (Mohanta et al. 2015). However, PIN protein does not have any conserved motifs in the loop (Křeček et al. 2009). A comparative study between PIN and PILS protein, has indicated that they share only 10-18% sequence identity (Feraru et al. 2012). These authors classified the PILS proteins based on the presence of generic phosphorylation site (non-kinase specific, viz serine, threonine and tyrosine), and kinase-specific phosphorylation site. Further, they grouped them as, (1) with less than ten phosphorylation sites (PILS5 and PILS7), (2) carrying between ten and fifteen sites (PILS2, and PILS6), and (3) which has more than fifteen phosphorylation sites (PILS1, PILS3 and PILS4). The grouping of PILS based on the phosphorylation site indicates their functional diversification and shows that phosphorylation based mechanisms might play a crucial role in their functional diversity. Although the hydrophilic loop is variable in nature, but the presence of a conserved threonine residue in the hydrophilic loop is the most likely target phosphorylation site for upstream kinases (Mohanta et al. 2015). Except AtPILS4, all PILS proteins of *A. thaliana* localize to the membrane of sub-cellular compartment endoplasmic reticulum (Barbez et al. 2012). Studies with the N-and C-terminal fusion proteins of AtPILS4 revealed their absence from ER or the plasma membrane. Similar to the AtPILS, OsPILS proteins of *O. sativa* also localize to the sub-cellular compartments. The OsPILS2, OsPILS5, OsPILS6b and OsPILS7a localize to the endoplasmic reticulum whereas OsPILS1 and OsPILS6a localizes to the vacuole and OsPILS7b localize to the plasma membrane and in endoplasmic reticulum (Table 2) (Mohanta et al. 2015).

6.2. Regulation and function of PILS

Barbez et al. (2012) reported that *AtPILS* genes are broadly expressed in various tissues, including seedlings, rosette leaves, stems, cauline leaves, flowers and siliquae (Barbez et al. 2012). Except *AtPILS1*, all of the *AtPILS* express in seedlings, whereas the expression of *AtPILS1*, and *AtPILS5* was very low in rosette leaves. Lower expression levels were also detected in stems for *AtPILS1, AtPILS2, AtPILS3* and *AtPILS5*. In cauline leaves, the expression of *AtPIL1* was very less and in siliquae low expression was observed for *AtPILS1, AtPILS5* and *AtPILS7* (Barbez et al. 2012). Barbez et al. (2012) demonstrated that the expressions of *AtPILS2-AtPILS7* were transcriptionally up-regulated by auxin treatment in wild-type seedlings (Barbez et al. 2012). More specifically, *AtPILS2, AtPILS3* and *AtPILS5* were highly up-regulated suggesting their role in auxin-mediated signaling process. Rice seedlings treated with 5 μM IAA shows differential modulation of *OsPILS* genes. From the transcript analysis it was found that all *OsPILS* genes were up-regulated in leaf tissues, whereas same genes were down regulated in the 21 days old root tissues (Mohanta et al. 2015). This suggests that there is significant impact of OsPILS genes in plant development on 21 days (Mohanta et al. 2015). However, a significant variation in expressions of *OsPILS* genes was also observed in cytokinin treated leaf and root tissues (Mohanta et al. 2015).

The phytohormone mediated differential expression of *AtPILS* led Barbez et al. (2012) to deeply investigate their functional role in auxin signaling, by expressing *AtPILS1* and *AtPILS3* using viral *35S* constitutive promoter (Barbez et al. 2012). The ectopic expression of *AtPILS1* or *AtPILS3* produces dwarf and /or bushy plants with severe deformity in flower development (Table 2) (Barbez et al. 2012). The flowers displayed severe patterning defects with homeotic transformation of flower organs into new flower buds, unfused carpels and triplication of the gynoecium. The T1 generation of the over expressed *AtPILS1* and *AtPIL3* were

sterile. However, the over expressed *p35S::AtPIL5* lines produced moderately fertile flowers. *AtPILS2* and *AtPILS5* were abundantly expressed at the seedling stages; therefore mutant analysis was performed on these genes. They found enhanced hypocotyl growth in *pils2 pils5* double mutants. However, dark grown *p35S::PILS5:GFP* expressing plants had reduced hypocotyls. The *PILS2* and *PILS5* exhibits an overlapping expression in the root transition zone and *PILS5* gain of function experiments manifest in agravitropic growth of hypocotyls (Barbez et al. 2012). The *pils2* single mutant and the *pils2 pils5* double mutant makes longer roots than the wild-type seedlings, whereas over expression of *AtPILS5* results in relatively short roots (Barbez et al. 2012). The *pils2,* and *pils5* single mutant and the *pils2 pils5* double mutant display a higher lateral root density, whereas the *PILS5* gain-of-function mutant had reduced lateral roots. To understand the role of the auxin response element (AuxRE) DR5 in the *pils* mutant, *pils2-2* and *pils5-2* knockout mutants were expressed with *pDR5rev:GFP* (Barbez et al. 2012). Such plants display higher signal in lateral roots, but no alteration in the DR5 activity was seen in the main root tip. However, moderately expressing *p35S::PILS5::GFP* seedlings exhibit reduced auxin responses in the root tip and lateral root. It was observed that *pils2 pils5* loss-of-function mutant show hypersensitive root growth whereas *PILS5* gain-of-function mutant produces hyposensitive root growth (Barbez et al. 2012). The *pils2 pils5* double mutant had relatively higher auxin export activity which revealed a reduced auxin holding capacity in *pils2 pils5* loss-of-function mutants. In BY cell line study it was reported that the ratios of auxin-glutamate (Glu) to auxin-aspartate (Asp) conjugate shifted towards the free auxin in *pils2* and *pils5* loss-of-function mutants. The *p35S::PILS5::GFP* expressing line shows reduced auxin response in the root tip. A significant shift was found in the auxin-Glu and auxin-Asp to free auxin ratios in *p35S::PILS5::GFP* seedlings which indicates higher rate of auxin conjugation and hence conjugation-based auxin metabolism (Barbez et al. 2012). Study led by Béziat et al. (2017) reported the role of PILS protein in light mediated reduction in nuclear auxin signaling for transition of plant growth (Béziat et al. 2017). *PILS2* and *PILS5* lead to asymmetric gene expression during apical hook formation (Béziat et al. 2017). *pils2* single mutant show delayed onset of apical hook development whereas *pils1 pils2* double mutant show strong delay in apical hook formation (Béziat et al. 2017). However, *pils1 pils2 pils3* triple mutant do not show apical hook opening that might be due to functional divergence of distinct *PILS* genes (Béziat et al. 2017). In addition, PILS proteins also regulate the reduction of nuclear auxin signaling during apical hook formation (Béziat et al. 2017).

7. Conclusion and future perspective

The role of auxin signaling is of pivotal importance in plant growth, development, tropism and gravitropic responses. However, it has not been elucidated how PINs and ABCB proteins localize in the plasma membrane in a polar and non-polar fashion, respectively. Also localization of PILS to the endo-membrane is not clear. Understanding the molecular mechanisms that govern their polarity patterns and also their non-polar distribution is important. It is also important to study the role of various conserved motifs in different auxin transporter proteins to find out the possible auxin binding domains. It is also necessary to find the signaling sequences of AUX/LAX, PIN, ABCB and PILS proteins. The role of important signal sequences, including palmitoylation and myristoylation event cannot be ruled out for the localization of auxin transporters in the plasma membrane. Because palmitoylation and myristoylation events play a crucial role in membrane attachment and protein trafficking.

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