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# Plant Metal and Metalloid Transporters



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### The Role of ABC Transporters in Metal Transport in Plants

<mark>Siddhi Kashinath Jalmi</mark>

#### Abstract

The metal ions are very essential for the survival, being an important part of many biological processes; however excess of metals causes toxicity. Correct balance of metal ions is necessary in the acquisition of metals depending on physiological needs. The uptake and transport of the essential metals occur with the help of metal transporters, which are also involved in homeostasis of metals. The metal transporters are found to be localized in different cellular compartments in different tissues depending upon their uptake in root cells and transport from root to xylem and to shoot and sequestration in vacuole to maintain the homeostasis. Different classes of transporters which are involved in uptake, transport, and sequestration of metals are discussed of which ATP binding cassette (ABC) family of transporters in plants were identified in detoxification process where they exhibited important role in heavy metal detoxification and in metal homeostasis in cell. This chapter discusses the different subfamilies of ABC transporters and their role in metal transport and sequestration.

#### **Keywords**

ABC transporters  $\cdot$  Heavy metal toxicity  $\cdot$  Metal uptake  $\cdot$  Metal sequestration  $\cdot$  Phytoremediation

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#### 3.1 Introduction

The acquisition of metal ions is very essential for the survival of all the organisms as these metals are an important part of many biological processes and serves as cofactors as a component of metalloproteins. Deficiency of the metals causes growth retardation, and developmental defects in organisms and uptake of excess of metals cause toxicity. Hence, proper balance is necessary in the acquisition of metals depending on physiological needs. Like other organisms, plants show mechanisms to tightly regulate metal uptake, allocation, and storage. The essential metals like iron (Fe), zinc (Zn), manganese (Mn), and copper (Cu) are trace metals that are required only in traces usually less than one parts per million (ppm), and their accumulation leads to toxicity. Apart from these, nature does contain nonessential heavy metals that are toxic and interfere with transporters required for uptake and transport of essential metals. These heavy metals possess deleterious effects on environment and ecosystem and are accumulated in environment naturally due to volcanic eruption and anthropogenically due to mining, incinerations, the use of pesticides and fertilizers, etc. Heavy metals include arsenic (As), cadmium (Cd), chromium (Cr), iron (Fe), lead (Pb), mercury (Hg), silver (Ag), and zinc (Zn) (Phillips 1981).

The uptake and transport of the essential metals occur with the help of metal transporters, which are also involved in homeostasis of metals. Many of the heavy metals are known to hijack metal transporters for their uptake and transport. Plants have acquired specialized genetic and biochemical mechanism to sense and transport essential metals at proper physiological concentration and remove nonessential metals from the cellular environment (Verbruggen et al. 2009). The metal transporters are found to be localized in different cellular compartments in different tissues depending upon their uptake in root cells and transport from root to xylem and to shoot and sequestration in vacuole to maintain the homeostasis. Different classes of transporters which are involved in uptake, transport, and sequestration of metals are discussed below.

One of the major metal transporter families involved in metal uptake is ZIP family. The members of this family are zinc-regulated transporter (ZRT-like proteins) and iron-regulated transporter (IRT), and this is where the name of family arises (Claus and Chavarría-Krauser 2012). These transporters translocate divalent cations across the membrane such as Fe, Zn, Cd, Mn by IRT1, and Zn by ZRT1 and ZRT2 (Grotz et al. 1998; Vert et al. 2002). These cationic or divalent metal transporters also take part in transport of heavy metal Cd (Thomine et al. 2000). Another family of transporter associated with Cu transport and homeostasis is copper transporters (COPT), having transmembrane domains in protein. These are also involved in transport of Zn and Fe (Morel et al. 2009; Yuan et al. 2011) (Fig. 3.1).

Natural resistance-associated macrophage protein (NRAMP) transporters play an important role in divalent metal transport including heavy metals like Fe, Mn, Cu, Zn, Ni, Co, and Cd (Sasaki et al. 2012). In *Arabidopsis*, Fe, Mn, and Cd transport is carried out by NRAMP1, NRAMP3, and NRAMP4, wherein NRAMP1 is localized



**Fig. 3.1** Overview of metal transporters in various stages of metal transport and sequestration. The uptake of metal ions and their transport and sequestration occur in various stages. Firstly, the metals are mobilized by the roots by secretion of chelators and acidification of the soil surrounding the roots. After mobilization, metal ions are imported into the root cells by various transporters present on the cell membrane of root cells (as described in the figure). Following the metal absorption, metal ions are transported to the xylem parenchyma for the loading of xylem wherein a set of metal transporters are involved. Through the xylem, metals are transported to sink tissues wherein their sequestration in vacuoles takes place depending on the concentration and homeostasis of metal ions

in cell membrane of root cells and NRAMP3 and NRAMP4 are localized in tonoplast. NRAMP2 is studied to be involved in Fe transport, whereas Cd is transported by NRAMP6 (Sasaki et al. 2012; Bozzi and Gaudet 2021) (Fig. 3.1).

Apart from contribution of metal transporters in the uptake of metals by root cells, they also contribute in their transport from root to shoot. For this, the loading of the xylem from the adjacent parenchymal cells is necessary, which is performed by the transporters discussed below. One of the transporters contributing in root-to-shoot transport is heavy metal transporting P-type ATPase (HMAs). This transports metals within the cellular compartments, that is, from cytoplasm to xylem or from plasma membrane to organelles. Of these P-type ATPase, HMA2 transports Zn in developing tissues, and HMA3 transports Cd and is present in tonoplast; however, HMA4 plays a role in loading metal to xylem tissue (Hussain et al. 2004; Yamaji et al. 2013). P-type ATPase are the ATP-dependent ion transporters which are the largest

and most diverse transporters in terms of substrate specificity (Palmgren and Nissen 2011). These are also reported to xylem loading and shoot transport of heavy metal like Cd in addition to Zn (Ceasar et al. 2020) (Fig. 3.1).

Another family of transporters involving the root-to-shoot transport is multidrug toxic compound extrusion (MATE) family transporters. These are basically efflux proteins studied to detoxicate the cellular environment by extruding the toxic compounds out of the cell. These transporters mainly transport Fe from root to shoot and extrude Al out of cells. Example of transporter belonging to MATE class is citrate transporter which participates in loading of Fe and citrate in vascular tissues, in the form of ferric citrate complex (Durrett et al. 2007; Delhaize et al. 2012) (Fig. 3.1).

A family of transporter capable of transporting diverse range of substrates is oligopeptide transporter family (OPT), of which yellow strip protein 1 (YS1) is characterized in maize to be involved in transporting Fe, Zn, Ni Cu, Cd, and Mn. In rice, several identified OPTs are known to translocate chelated Fe (Lubkowitz 2011; Liu et al. 2012) (Fig. 3.1).

Whenever a metal ion is not utilized in any metabolic activity or if its concentration rises, then it is either transported to the apoplast or to vacuole in order to maintain homeostasis and avoid toxification of the cell. Here the role of several intracellular transporters comes into play. One of such transporters are ATP binding cassette (ABC) family of transporters, constituting the largest family of transporters, ranging from its presence from bacteria to eukaryotes. These are ATP-driven transporters containing transmembrane domains used in the transport of xenobiotics and chelated metals into vacuole (Henikoff et al. 1997; Wanke and Üner Kolukisaoglu 2010). Apart from ABC transporters, cation diffusion facilitator (CDF) family and HMA and NRAMP transporter family are also involved in sequestration of metals such as Pb, Zn, Co, Cd, and Fe into the vacuoles and vacuolar phosphate transporters (VPT1) involved in the intake of heavy metal As (Kawachi et al. 2008; Sasaki et al. 2012) (Fig. 3.1).

ABC transporters being the largest family of transporters, and despite of the availability of genome sequence of model plant *Arabidopsis*, the functional knowledge about this large ABC transporter family is still scarce. This chapter focuses on the role of ABC transporters in the metal transport and their sequestration in plants, giving information about the structure of ABC transporters and their localization in plants and their role in metal transport.

#### 3.2 ABC Transporter Family

As discussed above, ABC transporter constitutes largest family ranging from its presence in bacteria to humans, primarily serving as membrane-intrinsic primary activated pumps. ABC transporters are known to be transporters of diverse substances like lipids, carbohydrates, phytohormones, chlorophyll catabolites, xeno-biotic conjugates, and heavy metals across the cellular membrane. Observing their diverse role, these transporters are localized on diverse membrane like plasma

membrane, tonoplast, and mitochondrial, plastidial, and peroxisomal membrane, implicating their function in cellular secretion and vacuolar sequestration. The first ABC transporter to be studied was involved in nutrient uptake in bacteria and was called as prokaryotic periplasmic permease (Ames 1986). Much of the studies have been performed on other members of ABC transporter superfamily and are identified as transporters from human, yeast, and bacteria that mediate multiple drug resistance (MDR), also including cystic fibrosis transmembrane conductance regulator (CFTR) and sulfonylurea receptor (SUR) (Rommens et al. 1989; Aguilar-Bryan et al. 1995; Prasad et al. 1996). In addition to their importance in animals and other organisms, ABC transporters also have emerged as fascinating transporters in plants. In the review by Higgins in 1992, only one plant ABC transporter was reported. Two pioneering studies marking the start of research on plant ABC transporters describe the isolation of MDR homolog in Arabidopsis thaliana and transport of glutathione conjugate into the vacuole by MRP-like transporter in barley (Dudler and Hertig 1992; Martinoia et al. 1993). Currently, in model plant Arabidopsis and crop plant rice, there are around 120 members of ABCs identified. In Arabidopsis, there are nine subclasses of these transporters, namely, ABCA, ABCB, ABCC, ABCD, ABCE, ABCF, ABCG, ABCH, and ABCI, having different locations in cell, with involvement in different metal transports (Verrier et al. 2008). However, based on the size of the protein, orientation, and presence of transmembrane domain, plant ABC transporters can be classified into 13 subfamilies and are categorized into fullmolecule transporters, half-molecule transporters, and quarter molecule transporters (Rea 2007). ABC transporters being an important part of detoxification machinery are also recognized to participate in a range of physiological processes like polar auxin transport, hormonal regulation of abscisic acid (ABA), lipid metabolism, stomatal regulation, disease resistance, etc., allowing plant to cop up with environmental biotic and abiotic stresses (Geisler and Murphy 2006; Stein et al. 2006; Kang et al. 2010; Kuromori et al. 2010). ABC transporters exhibit peculiar features as compared to other families of transporters. Firstly, ABC transporters are ATP driven, but the form of ATP that is utilized is Mg-ATP and not the free ATP. However, other nucleoside triphosphates like UTP or GTP can partially be substituent for ATP in the transport process. Also, vanadate, a metastable analog of orthophosphate, can

transport process. Also, vanadate, a metastable analog of orthophosphate, can substitute for ATP thus affecting the transporters. Secondly, the transmembrane electrochemical potential difference does not affect the transport process by ABCs (Rea et al. 1998).

#### 3.3 Molecular Structure of ABC Transporters

Modular structure of ABC transporters includes four core structural domains consisting of two transmembrane domains (TMD) and two nucleotide folds (NBF). The TMD consist of multiple membrane spanning alpha helices, and NBF is involved in binding to ATP and its hydrolysis. In bacteria, these domains are encoded on different polypeptides by different genes and are thus called as half-size ABC transporters. While in eukaryotes, these transporters are encoded as one full

polypeptide, so-called as full-size transporters. Full-size transporters can be further divided based on their orientation as multidrug-resistant proteins (MDRPs), multidrug-resistant-like proteins (MRPs) having the topology of TMD-NBF-TMD-NBF, while the pleiotropic drug resistance (PDRs) and ABC-like proteins exhibit mirrored topology of NBF-TMD-NBF-TMD (Bungert et al. 2001) (Table 3.1). The NBF domain is made up of two conserved sequence motifs: one is ATP binding site consisting of two boxes Walker A and Walker B, separated by 120 amino acids of specific consensus sequence of ABC transporters. The NBF domain sequence exhibits 30–40% identity over a range of 200–400 amino acids among different ABC transporters (Martinoia et al. 2002; Linton 2007).

Sequencing of *Arabidopsis* genome has revealed the presence of 53 genes encoding full-size ABC transporters which seemed to be relatively more than ABC transporter genes found in yeast and mammals. This large number of ABC genes and higher sequence homology suggest functional redundancy (Martinoia et al. 2002; Rea 2007).

#### 3.4 Primary Superfamilies of Plant ABC Transporters

#### 3.4.1 MDR Superfamily

The first homolog of MDR to be cloned was AtPGP1 from *Arabidopsis*. AtPGP1 exhibit similar intron and exon structure and similar structural domain organization as that of mammalian homolog (Dudler and Hertig 1992). Another homolog AtPGP2 sharing 44% amino acid identity with AtPGP1 was cloned, and this showed 45% identity to mammalian MDR1 (Dudler and Sidler 1998). The function of AtPGP1 was demonstrated in hypocotyl cell elongation and export of peptide hormone from shoot apex. Homologs of mammalian MDR1 have also been reported in other plant species like PMDR1 in potato (showing 86% identical to AtPGP1/AtPGP2) and HvMDR1 and HvMDR2 in barley (showing 43% identical to AtPGP1/AtPGP2) (Wang et al. 1996; Davies et al. 1997). Much of the information about primary structure, topology, and domain organization can be revealed by comparing these homologs. Plant MDR proteins have significantly smaller molecular weight (between 134 and 144 kDa) than mammalian counterparts (~180 kDa) (Higgins 1992).

#### 3.4.2 MRP Superfamily

Investigations on the function of ABC transporters in xenobiotic detoxification led to the identification and characterization of MRP superfamily transporters (Rea et al. 1998). Based on the MRP members in mammals and yeast cadmium factor YCF1 (MRP1 homolog in yeast), search for the homologs was carried out in model plant *Arabidopsis* (Li et al. 1997). AtMRP1, AtMRP2, AtMRP3, AtMRP4, and AtMRP5 were cloned and identified to be the homologs, encoding glutathione-conjugated

	ABC		Domain	Transmembrane	
	subfamily	Protein members	orientation	domain	Localization
1	ABCA ATH (half size) and AOH (full size)	ABCA1 (full size) and ABCA2–ABCA12 (half size)	Forward orientation TMD- NBF- TMD- NBF	TM domain present	Not known
2	ABCB TAP/ HMT (half size) MDR/ DGP (full size)	ABCB1–ABCB7, ABCB9– ABCB22 (full size), and ABCB23– ABCB29-(half size)	Forward orientation TMD- NBF- TMD- NBF	TM domain present	Full-size proteins are localized to plasma membrane, and half-size proteins are localized to mitochondria; ABCB27 is localized in vacuolar membrane
3	ABCC MRP (full size)	ABCC1– ABCC15 (full size)	Forward orientation TMD- NBF- TMD- NBF	Additional TM domain (TMD0) present	Localized in vacuolar membrane
4	ABCD (PMP)	ABCD1 (full size) and ABCD2 (half size)	Forward orientation TMD- NBF- TMD- NBF	TM domain present	Localized in peroxisomes
5	ABCE/F RLI/GCN	ABCE1, ABCE2, and ABCE3 and ABCF1–ABCF5	-	Lack TM domain	Soluble cytosolic protein
6	ABCG PDR (full size) WBC (half size)	ABCG1– ABCG18 (half size), ABCG29– ABCG39, and ABCG43 (full size)	Reverse orientation NBF- TMD- NBF- TMD	TM domain present	Localized to plasma membrane except ABCG19
7	ABCH	Not identified in plant	s		
8	ABCI (bacterial type)	Seven members having only one TMD, ten members having only one NBF, four members having other domains	_	_	ABCI with NBF are localized to cytosol; rest ABCI are localized to mitochondria and chloroplast

 Table 3.1
 Subfamilies of ABC transporters in plants

transporters, located to be in tonoplast vesicles and isolated vacuoles (Lu et al. 1997, 1998; Marin et al. 1998; Sánchez-Fernández et al. 1998; Tommasini et al. 1998). AtMRP1 showed the highest transport capacity and is able to reduce the Cd sensitivity (Tommasini et al. 1998).

#### 3.5 Classes of Plant ABC Transporters

ABCA subfamily of Arabidopsis includes 12 proteins of which ABCA1 is orthologous to mammalian ABC1 and is a full-size protein having the large linker domain. The rest of 11 proteins in ABCA subfamily are half-size proteins missing the linker domain, and these are only found to be present in plants (Kovalchuk and Driessen 2010). ABCB subfamily contains 21 full-size and half-size proteins in Arabidopsis, which are much more than what is present in mammals (Lee et al. 2008). ABCC subfamily contains only full-size proteins, having N-terminal transmembrane domain, the role of which is not studied in plants; however, it has role in protein targeting in yeast and mammals (Klein et al. 2006). Arabidopsis ABCD subfamily contains one full-size ABCD1 and one half-size transporter (Hayashi et al. 2002). Members of ABCE subfamily include three proteins and that of ABCF include five proteins, and they have reported to be functioning as soluble proteins performing other functions like ribosomal recycling and not as transporters, since they lack transmembrane domain (Pisarev et al. 2010; Dong et al. 2017). ABCG subfamily is the largest subfamily having reverse orientation of NBF-MSD domain organization. This subfamily includes 12 full-size and 28 half-size proteins, and they have been identified to be present in plants, fungi, oomycetes, and even slime molds (Stein et al. 2006; Choi et al. 2011). ABCH subfamily also contains reverse orientation of domains; however, phylogenetically it is not related to ABCG and is not characterized in plants. ABCI subfamily have 21 members and are encoded as individual NBF as cytosolic protein lacking transmembrane domain (Zeng et al. 2017) (Table 3.1).

#### 3.6 Role of ABC Transporters

ABC transporters in bacteria were studied to be involved in transport of primary metabolites and export of lipids, enzymes like protease, lipases, antibiotics, cytotoxin, etc. In eukaryotes, ABC transporters were identified to play a role in cellular detoxification that helped in extrusion of toxic compounds from the cytosol. In plants, the first report stating ABC-mediated transport was observed in investigation of xenobiotic detoxification. In this study, it was noted that toxic compounds in plants get conjugated with glutathione tripeptide through thiol group, which are then transported to vacuole independently by vacuolar proton pumps. Xenobiotic detoxification is a multistep process, composed of stage 1 of activation, stage 2 of conjugation, and stage 3 of compartmentalization. In stage 1, the activation is caused by either the hydrolysis reaction by esterases and amidase or by oxidation reaction

by cytochrome P-450. This activation stage generates products with higher toxicity; however, it is an important step in detoxification since in this the functional groups are generated which are required in the next conjugation stage. In conjugation stage, the activated products of toxic compounds covalently linked to hydrophilic glucose/glutathione/malonate in substances like plants and glutathione/ glucuronate/sulfate in animals. In stage 3 of compartmentalization, the inactive water-soluble conjugates are transported from cytoplasm to compartments like vacuoles (Kreuz et al. 1996; Coleman et al. 1997). In animals, these conjugated compounds are secreted out of the cell through the plasma membrane, with the help of specific ATPase. However, in plants, these compounds are transported into the vacuoles, wherein they can be further metabolized. The transport to the vacuoles in plants is mediated by Mg-ATP-dependent transporters and not by nonhydrolyzable ATP or by inorganic phosphate (PPi). These pumps later were identified to be vacuolar glutathione-conjugate ABC transporters ABCC1 and ABCC2, performing transport of conjugated toxin to the vacuole (Martinoia et al. 1993; Kreuz et al. 1996). Both these ABCC transporters are involved in the transport of a broad range of glutathione conjugates. Arabidopsis ABCC1 is also studied to be an efficient transporter of folate which is known to be stored in vacuole and is necessary for methylation processes (Raichaudhuri et al. 2009). Initial stages of detoxification are similar in plants and animals, wherein cytochrome P450, glutathione-S-transferase, and glycosyltransferase are involved in conjugation. But in later processes in animals, conjugated toxic compounds are excreted out, whereas in plants, they are internalized in large central vacuole (Lu et al. 1998).

In eukaryotes, the ABC transporters are studied to perform transport in both directions irrespective of the side of the presence of NBF domain and the substrate (Shitan et al. 2003). Originally ABC transporters in plants were identified in detoxification process where they exhibited important role in heavy metal detoxification and in metal homeostasis in cell. However, apart from metal detoxification, ABC transporters are involved in diverse processes like transport of phytohormones, phytate accumulation in seed, and surface lipid deposition; hence, they play an important role in plant growth and development and stress management (Martinoia et al. 2002).

#### 3.6.1 Role in Growth and Development: Transport of Hormones, Fatty Acids, and Phytate

Other than toxic compound, ABC transporters have role in transport of important compounds like fatty acids, hormones, phytates, etc. Phytohormones serve to be crucial components of plant growth and development; hence, their biosynthesis and transport become vital for their proper function. For example, indole-3-acetic acid (auxin) is a central phytohormone performing many developmental processes like shoot development, lateral root formation, floral bud development, phototropism, and gravitropism. This is produced in shoot apical meristem and transported throughout the plant via xylem parenchyma cell-cell transport (Vanneste and Friml

2009). The cellular import and polar export of auxin are performed by two vital transporters, AUX1/LAX family and PIN family, respectively (Kramer 2004). In addition to these transporters, two ABC plasma membrane intrinsic ABC transporters ABCB1 and ABCB19 also contribute to intercellular auxin transport. It has been studied that ABC transporters and PIN proteins interact and modulate overall auxin transport activity (Geisler et al. 2005; Blakeslee et al. 2007). Besides auxins, ABC transporters transport stress hormone ABA from the site of its production, that is, from vascular tissues of root and shoot to foliar tissues. ABCG half-size transporter ABCG25, which is expressed in vascular parenchyma of root and shoot, exports ABA and shows high affinity to ABA (Kuromori et al. 2010). ABCG40 is involved in import of ABA across the stomatal plasma membrane which is also implicated in heavy metal resistance. Owing to the role of ABCG40, it is localized in stomatal plasma membrane along with another transporter ABCB14, regulating the import of apoplastic malate (Lee et al. 2008).

As noted earlier, ABC transporters are also involved in fatty acid transport from cytosol to peroxisomes, where fatty acids are involved in production of acetyl CoA. A study in *Arabidopsis* reported the role of ABCD1 in fatty acid import in peroxisomes (Zolman et al. 2001). The fatty acids are also important components of cuticle in plants, which is a protective layer covering the epidermis of aerial organs in plants. Cuticle formation is also necessary for proper organ development and in maintaining the morphology of organs. Two half-size ABC transporters, ABCG11/ABCG12, play a crucial role in cuticle formation (Pighin et al. 2004).

#### 3.6.2 Role in Pathogen Defense

Plant's secondary metabolites are considered to be important in pathogen defense, giving first line of defense against host and nonhost pathogens. Plants produce these metabolites and transport them to different plant parts like aerial surfaces, rhizospheric region, and apoplast and near the site of infection. This transport is studied to be mediated by a number of full-size ABC transporters of ABCG subfamily. ABCG30 mutation resulted in change in microflora in the plant's rhizosphere, which suggested the change in root exudate composition due to nonfunctionality of ABCG transporter. Apart from this, six other full-size ABC transporters and a half-size transporter were involved in transport and secretion of root exudates, mutation of which resulted in the alteration of plant's secondary metabolites in root exudate (Badri et al. 2008, 2009). The putative role of ABC transporter in pathogen defense was suggested in expression analysis of ABC transporters in response to biotic stress hormones SA and JA (Moons 2008). A full-size ABCG transporter PDR1 was reported to be the first transporter involved in active transport of terpenoids in plants, thus imparting defense against pathogen (Jasiński et al. 2001). This transporter is found to be overexpressed in the leaf epidermis, trichomes, petals, and roots, and its transcripts get induced upon the treatment of terpenoids, SA and JA. Mutation or downregulation of PDR1 causes plant susceptible to nonhost necrotrophic pathogens (Stukkens et al. 2005). Another study suggested the role of ABCG38/PDR8 in nonhost resistance, wherein the mutation of this transporter increased the susceptibility toward nonhost pathogens; however, it provided hypersensitivity against compatible host pathogen (Stein et al. 2006).

Besides acting as pathogen repellent, plant's secondary metabolites like isoflavonoids also act as attractant for beneficial microbes and plant-derived signaling molecules for establishing symbiosis with rhizobia, mycorrhizae, etc., thus helping in promoting the plant growth (Sugiyama et al. 2008). Considering the role of ABC transporters in transporting plant's secondary metabolites, it can be also assumed that these transporters play a role in defense against herbivores.

#### 3.7 ABC Transporters in Metal Transport and Sequestration

Although the ABC transporters have extended role other than transporting metals and heavy metals, however, involvement of ABC transporters in detoxification mechanism has been always a focal point, taking into consideration the metal contamination of agricultural soils becoming a serious problem. In this section, we will focus on function of metal, the role of ABC transporters in *Arabidopsis*, and some other plant species. ABC transporters present on plasma membrane are involved in metal uptake and transport, while those present on vacuolar membrane are involved in detoxification. Most of ABC transporters found in the vacuolar membrane belong to ABCC subfamily.

The detoxification of metal by ABC transporters on vacuolar membrane in plants is largely dependent on formation of phytochelatin (PC), that is, the peptide-type chelators, which are synthesized by heavy metal-activated phytochelatin synthase from glutathione (Cobbett 2000). These PCs are produced in response to increased level of metals and heavy metals in plants. The first metal phytochelatin transporter that was identified in tonoplast membrane of yeast was HMT1, of which the homologs have been studied in animals while its homolog has not been identified in vacuolar membrane of plants (Ortiz et al. 1995; Schwartz et al. 2010). However, a mitochondrial ABC transporter ABCB25 that is involved in biogenesis of iron-sulfur (Fe-S) cluster and biosynthesis of molybdenum cofactor in plants is studied to be close homolog of HMT of yeast. ABCB25 is also involved in transport of glutathione-Cd, Cd-S, and Fe-S from mitochondria to cytosol (Kim et al. 2007) (Fig. 3.2).

After a long time of identification of vacuolar phytochelatin transporter in yeast, Song and his team in 2010 succeeded in identifying the vacuolar phytochelatin transporters in plants. These were two ABCC proteins ABCC1 and ABCC2, having redundant function identified in *Arabidopsis*. These were studied to be main important transporters of arsenic-PC complex. The ABCC1/2 showed marginal effect in arsenic stress tolerance in *Arabidopsis* (Song et al. 2010). The study suggested that to obtain tolerance to arsenic overexpression of both ABCC transporter and PC synthase was mandatory and not of just the ABCC transporters (Song et al. 2014a, b). Subsequently, the role of these ABCC1 and ABCC2 was identified in



**Fig. 3.2** Metal transport and sequestration by ABC transporters. The members of ABC transporter family playing an important role in metal transport and sequestration are described in this figure. Several ABC transporters are known to be localized on cell membrane (mainly ABCG and ABCI subfamily) importing metals inside the root cell from the soil. Some ABC transporters ABCB and ABCC subfamily present on vacuolar membrane are involved in sequestration of metals. Also, ABC transporters are found to be present on mitochondrial membrane transporting metals in and out of mitochondria

vacuolar sequestration of cadmium and mercury, thus providing tolerance to Cd and Hg stress (Park et al. 2012) (Fig. 3.2). The homolog of ABCC1 in yeast is yeast cadmium factor (YCF1) which was the first transporter identified to be involved in heavy metal resistance. YCF1 mediate the transport of glutathione metal complexes for As and Cd, similar to its function in plants (Ghosh et al. 1999). The transport of Cd is also exhibited by other two proteins of ABCC family ABCC3 and ABCC6; however, the mechanism of transport is not examined in plants (Wanke and Üner Kolukisaoglu 2010). Apart from these, ABCB family member, ALS1, found to be localized on vacuolar membrane performs the transport of aluminum in rice (Huang et al. 2012) (Fig. 3.2).

In addition to their prominent role in exporting metals to vacuole for sequestration, some of ABC transporters have shown their role in metal uptake from soil. These transporters belong to ABCG subfamily and bacterial-type ABC subfamily having their localization on plasma membrane vesicle of root cells. The bacterialtype ABC proteins are STAR1 and STAR2 that play a crucial role in imparting tolerance to aluminum stress in rice. STAR1 corresponds to nucleotide binding domain whereas STAR2 corresponds to transmembrane domain, where both these domains make single functional transporter protein (Huang et al. 2009). ABCG subfamily transporter, ABCG36, also called as PDR8/PEN3 is also reported to be localized at plasma membrane which was upregulated in response to Cd metal, and its overexpression imparted tolerance to Cd metal stress (Stein et al. 2006) (Fig. 3.2). Apart from metal transport, ABCG36 also exhibits an important role in defense against pathogen (Stein et al. 2006).

Another member of ABCG family, ABCG40/PDR12, was studied to be involved in lead detoxification; this fact was proven by using the overexpression and mutant lines of ABCG40, wherein overexpression lines were more tolerant and accumulated less Pb while mutant lines were more sensitive and accumulated more Pb inside the plants (Lee et al. 2005) (Fig. 3.2). This Pb tolerance driven by ABCG40 may be due to direct transport of Pb causing its detoxification or may be due to uptake of stress hormone ABA (Kang et al. 2010).

AtATM3 is an ATP binding cassette transporter from *Arabidopsis* and was studied to be involved in biogenesis of iron-sulfur cluster and iron homeostasis in plants. AtATM3 is a mitochondrial protein and was seen to be upregulated in root cells of plants treated with lead and cadmium and imparted tolerance to Pb and Cd heavy metals (Kim et al. 2006) (Fig. 3.2).

#### 3.8 Future Prospects

Heavy metal contamination and its toxicity have posed serious effects on the agriculture and the health of living organisms. For past many years, efforts have been made to develop plants that are able to accumulate large amounts of heavy metals and at same time produce high biomass. Observing the roles of these ABC transporters in metal uptake and sequestration, researchers are trying to make use of these in phytoremediation of metal-contaminated sites. Approaches being used are either overexpressing these metal transporters or producing higher amount of glutathione or phytochelatin in plants. Looking at the promising role of yeast ABC transporter YCF1 in heavy metal sequestration in various plants, transgenic popular plants overexpressing YCF1 are produced. These plants are capable of accumulating much of Cd from contaminated soils and were found to be much more tolerant and produced higher biomass (Shim et al. 2013). These transgenic popular trees due to their larger root system are efficient for long-term stabilization of metal-polluted soils. The use of the metal transporters particularly ABC transporters will provide useful tools for genetic engineering of plant with enhanced metal accumulation and tolerance, with their efficient use in phytoremediation.

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