Annals of Botany **106**: 199–203, 2010
doi:10.1093/aob/mcq115, available online at www.aob.oxfordjournals.org

ANNALS OF BOTANY
Founded 1887

REVIEW: PART OF A HIGHLIGHT SECTION ON PLANT–SOIL INTERACTIONS AT LOW PH

How a microbial drug transporter became essential for crop cultivation on acid soils: aluminium tolerance conferred by the multidrug and toxic compound extrusion (MATE) family

Jurandir V. Magalhaes*

Embrapa Maize and Sorghum, MG 424, Km 65, 35701-970, Sete Lagoas, Minas Gerais, Brazil
** E-mail jurandir@cnpms.embrapa.br*

Received: 25 March 2010 Returned for revision: 8 April 2010 Accepted: 4 May 2010 Published electronically: 28 May 2010

• *Background* Aluminium (Al) toxicity is a major agricultural constraint for crop cultivation on acid soils, which comprise a large portion of the world's arable land. One of the most widely accepted mechanisms of Al tolerance in plants is based on Al-activated organic acid release into the rhizosphere, with organic acids forming stable, non-toxic complexes with Al. This mechanism has recently been validated by the isolation of *bona-fide* Al-tolerance genes in crop species, which encode membrane transporters that mediate Al-activated organic acid release leading to Al exclusion from root apices. In crop species such as sorghum and barley, members in the multidrug and toxic compound extrusion (MATE) family underlie Al tolerance by a mechanism based on Al-activated citrate release.
• *Scope and Conclusions* The study of Al tolerance in plants as conferred by MATE family members is in its infancy. Therefore, much is yet to be discovered about the functional diversity and evolutionary dynamics that led MATE proteins to acquire transport properties conducive to Al tolerance in plants. In this paper we review the major characteristics of transporters in the MATE family and will relate this knowledge to Al tolerance in plants. The MATE family is clearly extremely flexible with respect to substrate specificity, which raises the possibility that Al tolerance as encoded by MATE proteins may not be restricted to Al-activated citrate release in plant species. There are also indications that regulatory loci may be of pivotal importance to fully explore the potential for Al-tolerance improvement based on MATE genes.

Key words: Aluminium tolerance, multidrug and toxic compound extrusion, MATE, membrane transporters, regulation of gene expression, abiotic stress, microbial.

INTRODUCTION

A mechanism of aluminium (Al) tolerance in plants, which is based on the release of organic acids into the rhizosphere, has long been hypothesized as a result of a substantial body of physiological evidence indicating that roots of Al-tolerant plants can release these organic compounds in response to Al. Organic acids have the ability to exclude this metal from sensitive sites in the root apex resulting in the formation of stable complexes with Al. However, it was only 6 years ago, in 2004, that the first major Al-tolerance gene, *ALMT1*, was cloned in wheat (Sasaki *et al.*, 2004), lending molecular validation to the organic acid hypothesis. ALMT1 was found to be an Al-activated malate transporter, which belongs to a novel membrane protein family, and was later found to confer Al tolerance to other species in addition to wheat. In 2007, new insights into the molecular basis of Al tolerance in plants occurred with the publication of research findings implicating multidrug and toxic compound extrusion (MATE) proteins as major determinants of Al tolerance in plants. In sorghum, *SbMATE*, the gene underlying a major Al-tolerance locus, Alt_{SB}, was identified and shown to be a member in the MATE family. This transporter confers Al tolerance by a physiological mechanism based on Al-activated citrate release into the rhizosphere (Magalhaes *et al.*, 2007). In barley, another MATE protein, HvAACT1 was found to be an Al-activated citrate transporter that confers barley Al tolerance (Furukawa *et al.*, 2007).

Interestingly, *FRD3*, a MATE family member that was originally implicated in iron nutrition in arabidopsis (Green and Rogers, 2004) was also found to mediate citrate efflux into the root vascular tissue; citrate has thus been proposed to act as an iron chelator with a role in iron distribution in the plant (Durrett *et al.*, 2007). The fact that *FRD3* shares significant sequence identity with the Al-tolerance genes in sorghum and barley raises interesting questions concerning the nature and the evolution of the causative mutations that confer Al tolerance in plants. In the course of evolution, these mutations may conceivably have conferred very specific structural changes to some MATE proteins to create, for instance, Al-specific binding sites enabling Al-dependent transport activity, thus creating *bona fide* Al-tolerance genes. Alternatively, Al tolerance might merely be one of the many outcomes of a highly diverse and ubiquitous gene family, with Al tolerance resulting from the activity of polyspecific transporters. In the genomics era, association analysis in concert with detailed physiological and molecular investigations provides a means to dissect the fine structure of a locus into quantitative trait nucleotides. The nature of Al-tolerance quantitative trait nucleotides remains unknown

but it is nevertheless envisaged that novel molecular breeding strategies, based on MATE genes, will be developed as the relationship between the structure of these genes and their function in providing Al tolerance is elucidated. However, at the moment, some expectations can be formed based on the global knowledge of MATE proteins, which are by no means restricted to plants but rather are strikingly distributed throughout all domains of life. Here, we review the major characteristics of MATE genes and will discuss them with regards to the Al-tolerance phenotype in plants.

THE PHYLOGENY OF THE MATE FAMILY AND *NorM*, THE PRIMORDIAL MATE

One of the most important mechanisms for drug resistance in prokaryotes and eukaryotes involves efflux of toxic compounds from the cell. These efflux systems belong to five transporter families: namely the major facilitator superfamily (MFS), the ATP-binding cassette (ABC) superfamily, the drug metabolite transporter (DMT) superfamily, the resistance/nodulation/division (RND) superfamily and the multidrug and toxin extrusion (MATE) family (Saier and Paulsen, 2001), with the last family of transporters functioning as secondary carriers that depend on an transmembrane electrochemical gradient for extrusion activity. MATE proteins range from approx. 400–700 amino acid residues in size and a typical characteristic of this family is the presence of 12 transmembrane helices (TM) (Omote *et al.*, 2006). In addition, long N and C tails exposed to the cytoplasm suggest the possibility of interactions with other proteins (Moriyama *et al.*, 2008). Accordingly, no consensus sequences appear to be conserved across all MATE members, which share approx. 40 % sequence similarity, although slightly conserved regions are found near TM1 and TM7, in extracellular loops between TM1 and TM2, and TM7 and TM8, in cytoplasmic loops between TM2 and TM3, and TM8 and TM9, and in loops between TM4 and TM5, and TM10 and TM11. MATEs are ubiquitously distributed in all domains of life and the family includes >1000 proteins (Moriyama *et al.*, 2008). Accordingly, a phylogenetic analysis with MATE members highlighted three large families and 14 subfamilies. Class 1 comprises bacterial MATEs, class 2 comprises eukaryote MATEs and class 3 includes bacterial and archaeal MATEs. Thus, the clustering of MATE proteins is in general consistent with organismal phylogeny. Furthermore, class 2 MATEs are divided into four subclasses: (1) yeast and fungi, (2) plant, (3) protozoan and (4) animal. A previous phylogenetic analysis undertaken by Hvorup *et al.* (2003) highlighted 15 subfamilies within which seven were bacterial specific, three comprised both archaeal and bacterial proteins, one was archaeal specific, one included bacterial and plant proteins and three subfamilies consisted of eukaryote proteins from yeast, animal and plants (Hvorup *et al.*, 2003). One of these subfamilies was composed largely of arabidopsis homologues and this plant species was found to possess 58 MATE paralogues (Li *et al.*, 2002; Hvorup *et al.*, 2003). A large number of MATE paralogues – exceeding 40 – has also been reported in *Medicago truncatula* (Zhao and Dixon, 2009). Sequence alignments in arabidopsis identified the conserved sequences as CGQA, located between TM2 and TM3, and RVSNXLGA in TM8 (Li *et al.*, 2002). Based on sequence similarity to the prokaryotic polysaccharide transporter (PST) family within the multidrug/oligosaccharidyl-lipid/polysaccharide (MOP) exporter superfamily, to which the MATE family was placed, MATE precursors were hypothesized to be complex carbohydrate exporters in prokaryotes with 6 TMs, which underwent internal duplication to generate a 12 TM protein (Hvorup *et al.*, 2003). Finally, symmetric repetition of conserved regions in the N- and C- terminal halves of MATE proteins suggests a common ancestry to the MATE family (Omote *et al.*, 2006).

The first MATE gene isolated was *NorM* in *Vibrio parahaemolyticus*, and NorM was found to be a multidrug efflux protein that conferred resistance to norfloxacin and other antimicrobial agents by Na^+/drug antiport (Morita *et al.*, 1998, 2000). On the basis of 12 TMs present in NorM, the encoding gene was first hypothesized to be a member of the Major Facilitator Superfamily. However, because neither NorM nor its homologue in *Escherichia coli*, YdhE, were found to share significant similarity with MFS members, Brown *et al.* (1999) concluded NorM was a prototype of a previously unidentified family, thereby designated the MATE family.

FUNCTIONAL DIVERSITY IN THE MATE FAMILY

In addition to NorM, which confers resistance to structurally unrelated compounds, several proteins in the MATE family have been implicated in a variety of functions related to cell protection from toxins. Two DinF proteins from *E. coli* and *S. pneumoniae*, whose expression is DNA damage-inducible, were also found to be related to NorM (Brown *et al.*, 1999) and DinF proteins have also been shown to be involved with bacterial virulence in tomato (Brown *et al.*, 2007), presumably due to a protection mechanism based on the efflux of antimicrobial compounds. Also, *ERC1* in yeast confers resistance to the methionine analogue, ethionine (Shiomi *et al.* 1991; Brown *et al.*, 1999), which is likely to result from the sequestration of *S*-adenosylethionine into the vacuole (Diener *et al.*, 2001). The *eds5* mutant in arabidopsis does not accumulate salicylic acid in response to biotic or abiotic stresses (Nawrath *et al.*, 2002). EDS5 was found to be homologous to DinF of *E. coli* and plays an important role in the salicylic acid-dependent pathway of plant defence against pathogens. The arabidopsis MATE gene, *ALF5*, is expressed in the root epidermis and cortex, and was found to restore normal lateral root growth in seedlings cultivated in bacto agar (Diener *et al.*, 2001). The *alf5* mutant plants were sensitive to contaminants present in the media, and ALF5 was thus thought to act in cellular detoxification by means of vacuolar sequestration or cellular efflux of toxic compounds.

In arabidopsis, loss-of-function mutations in genes belonging to the core flavonoid or proanthocyanidin branch convert the dark-brown wild-type seed colour into transparent testa mutants (Chai *et al.*, 2009). From this mutant the *TRANSPARENT TESTA12* (*TT12*) gene was cloned and found to encode a MATE family member that epistatically interacts with other genes in the flavonoid pathway, being expressed in ovules and developing seeds (Debeaujon *et al.*, 2001). Marinova *et al.* (2007) showed that the TT12

transporter is expressed in the tonoplast and based on transport analysis in heterologous systems, is a vacuolar flavonoid/H^+ antiporter. In addition, tight regulation of *TT12* expression was observed as *TT12* promoter activity (Marinova *et al.*, 2007) was observed specifically in proanthocyanidin-synthesizing cells. These authors raised the possibility that the functional uniqueness of TT12 as a flavonoid transporter in arabidopsis is related to this highly specific expression pattern. Interestingly, activation tagging in tomato identified an MYB transcription factor involved in anthocyanin accumulation (Mathews *et al.*, 2003). In this work the *MYB* gene was also found to up-regulate a putative permease similar to TT12 in tomato, and in arabidopsis *TT12* was found to be regulated by three regulatory loci, *TT2* encoding a R2R3-MYB protein, *TT8* encoding a bHLH protein, and *TTG1* corresponding to a WDR protein, which play a role in proanthocyanidin biosynthesis (Lepiniec *et al.*, 2006; Zhao and Dixon, 2009). This suggests that at least part of the specificity of function for MATE genes may arise from the activity of possibly complex regulatory networks. Two MATE genes in grapevine are also likely to promote vacuolar transport of anthocyanins, and, analogous to the aforementioned cases, the grape MATEs are expressed more specifically in anthocyanin-synthesizing tissues (Gomez *et al.*, 2009). Another example of strong regulatory effects affecting the expression of MATE genes was found in tobacco roots, where *NtMATE1* and *NtMATE2*, along with genes in the nicotine biosynthetic pathway, are co-ordinately regulated by *NIC* regulatory loci to sequester the alkaloid compound in the vacuole (Shoji *et al.*, 2009). Similar co-regulation was found by Morita *et al.* (2009) for *Nt-JAT1*, which was nonetheless expressed ubiquitously in tobacco. Interestingly, the microbial MATEs, *NorM* and *YdhE*, appear to confer resistance to berberine, a common plant alkaloid (Morita *et al.*, 1998). This function appears to be conserved in plants as AtDTX1 in arabidopsis was also found to mediate efflux of berberine (Li *et al.*, 2002) and a similar mechanism based on H^+ antiport is possibly encoded by a MATE gene in the medicinal plant, *Coptis japonica* (Otani *et al.*, 2005; Moriyama *et al.*, 2008).

Mammalian MATEs function as H^+ antiporters to transport organic cations and are involved in a variety of functions (Moriyama *et al.*, 2008). Otsuka *et al.* (2005) identified the *MATE1* gene in humans, which is predominantly expressed in kidney and liver and was proposed to be the final step of organic cation efflux by means of H^+ antiport. Accordingly, *cis*-inhibition studies with a wide variety of metabolites indicated MATE1-mediated transport of organic cations to be polyspecific in nature. The mouse orthologue, *mMATE1*, showed characteristics very similar to *MATE1* in humans, but its expression was widely distributed in various tissues in addition to kidney and liver, suggesting involvement in various biological functions (Hiasa *et al.*, 2006).

Al TOLERANCE SPECIFICITY AND THE MATE FAMILY

Although MATE proteins have been initially reported to show preference for hydrophobic cations (Eckardt, 2001), the rather polyspecific nature of MATE transporters has now become clear. For instance, mammalian MATEs have been shown to transport zwitterionic and anionic compounds in addition to cationic compounds (Tanihara *et al.*, 2007). Plant MATEs that have been implicated in citrate transport are FRD3 in arabidopsis (Durrett *et al.*, 2007), SbMATE in sorghum (Magalhaes *et al.*, 2007), HvAACT1 in barley (Furukawa *et al.*, 2007), OsFRDL1 in rice (Yokosho *et al.*, 2009), AtMATE in arabidopsis (Liu *et al.*, 2009), ZmMATE1 in maize (Maron *et al.*, 2009) and a MATE gene was also implicated in citrate efflux in wheat (Ryan *et al.*, 2009). In addition, *SbMATE* is similar to *LaMATE* that is expressed in proteiod roots in white lupin under phosphorus deficiency (Uhde-Stone *et al.*, 2005; Magalhaes *et al.*, 2007), suggesting a possible role in citrate transport for LaMATE. It should be noted, however, that these studies were largely hypothesis-driven and did not include a thorough examination of substrate specificity for the respective MATE proteins. Therefore, at this point there are no reasons to rule out the possibility that plant MATEs could transport substrates other than citrate, which may also play a role in Al tolerance. In fact, several indirect reasons point in that direction. For instance, phenolic compounds can form stable complexes with Al^{3+}, possibly playing a role in Al tolerance (reviewed by Kochian *et al.*, 2004; Tolrà *et al.*, 2009). However, given the documented involvement of MATE proteins in the transport of compounds such as alkaloids and flavonoids, it is possible that citrate-transporting MATEs may have acquired dual transport functions, also enabling transport of phenolic compounds. Alternatively, other members of the MATE family may have specifically diverged to confer Al tolerance by a physiological mechanism based on phenolics. In fact, a bacterial mutant complemented with AtDTX1 from arabidopsis, which has been shown to mediate efflux of plant alkaloids among other toxic compounds, became resistant to Cd^{2+}, although no effect was observed in the presence of Al^{3+} (Li *et al.*, 2002). In addition, for two MATE homologues in maize, *ZmMATE1* and *ZmMATE2*, which colocalize to two major Al-tolerance quantitative trait loci, only the former is a citrate transporter whereas *ZmMATE2* may be involved in a novel Al-tolerance mechanism (Maron *et al.*, 2009), possibly mediating transport of a different compound.

Some plant species appear to utilize internal mechanisms of Al detoxification. Buckwheat can accumulate Al and it has been shown that Al is present in leaves and roots as an Al : oxalate complex (Ma *et al.*, 1998). In addition, Al in the xylem sap was found to be complexed with citrate (Ma and Hiradate, 2000), suggesting that Al undergoes a ligand exchange from oxalate to citrate when it is transported to the xylem, and exchanged back into oxalate when transported to the leaves (Kochian *et al.*, 2004). It is interesting that two MATE homologues appear to be involved in citrate efflux into vascular tissue. Those are FRD3 in arabidopsis (Durrett *et al.*, 2007) and OsFRDL1 in rice (Yokosho *et al.*, 2009), which are both localized to the pericycle cells of roots and appear to be necessary for efficient Fe translocation to the shoots. Therefore, considering various examples of tonoplastic MATEs, it will not be surprising if MATE homologues involved with internal transport of citrate are found to play a role in plant Al tolerance by an internal detoxification mechanism involving Al sequestration into the vacuoles. Indeed, most of the Al : oxalate complex in buckwheat was found to be

sequestered into vacuoles (Shen *et al.*, 2002), which is an accepted mechanism of internal detoxification (Ma, 2007). In addition, an ABC transporter has been suggested to play a role in arabidopsis Al tolerance and has been proposed to mediate Al redistribution from sensitive tissues (Larsen *et al.*, 2005). Subsequently, the same researches identified ALS1, a half-type ABC transporter, which is localized to the tonoplast and thought to be involved in Al sequestration in arabidopsis (Larsen *et al.*, 2007)

Examples have been presented indicating that the expression patterns of MATE genes involved with flavonoid transport are influenced by regulatory loci. Expression of *AtMATE*, which confers Al tolerance in arabidopsis by a mechanism based on Al-activated root citrate exudation, has been found to depend on *STOP1* (Liu *et al.*, 2009), a zinc finger transcription factor involved with tolerance to protons in arabidopsis (Iuchi *et al.*, 2007). In fact, *STOP1* appears to be involved in signal transduction pathways regulating a number of Al- and H^+-responsive genes in arabidopsis (Sawaki *et al.*, 2009), revealing a broader effect that goes beyond that in *AtMATE* and *AtALMT1* (Liu *et al.*, 2009). In rice, another transcription factor similar to *AtSTOP1*, *ART1*, regulates the expression of several genes possibly involved with Al tolerance. In addition, ART1 has been shown to interact with the promoter of the region of *STAR1*, which is involved with Al tolerance in rice (Yamaji *et al.*, 2009).

CONCLUSIONS

The MATE family has been shown to be ubiquitously distributed and extremely flexible in function. Although the study of plant MATEs is in its infancy, the importance of regulatory loci controlling MATE function appears pivotal. FRD3 in arabidopsis and OsFRDL1 in rice are both localized to the pericycle cells of roots and are likely to be involved with Fe translocation to the shoot (Durrett *et al.*, 2007; Yokosho *et al.*, 2009). In a study with a knockout mutant, OsFRDL1 was not found to confer Al-induced citrate release in rice (Yokosho *et al.*, 2009). However, when ectopically expressed under the control of the 35S promoter, arabidopsis FRD3 was found to confer Al tolerance by a mechanism involving citrate release from the roots (Durrett *et al.*, 2007), although apparently not in an Al-activated fashion. Therefore, it is possible that Al-tolerance mutations may have arisen to drive expression of functional transporters to Al-sensitive sites in the plant, which is widely accepted to be the root apex. Nevertheless, at this point it is still not possible to rule out the existence of specific structural features that tie together MATE activity and Al tolerance. For example, in arabidopsis, MATE members other than *AtMATE* and *AtFRD3* lack a large intracellular loop, which led Liu *et al.* (2009) to speculate on a specific role for this loop in citrate binding and transmembrane transport.

In sorghum, the correlation between SbMATE expression and Al tolerance in a panel including an allelic series at the underlying locus was extremely high (Magalhaes *et al.*, 2007), indicating that allelic effects are likely to be regulatory in nature. Similarly in barley cultivars differing in Al tolerance, *HvAACT1* expression was correlated with citrate release (Furukawa *et al.*, 2007). Considering that a transcription factor has been identified that modulates the expression of plant MATEs, further research should be directed towards identification and characterization of possible regulatory networks within a breeding perspective in crop species. This effort could reconcile a long-standing question in plant Al tolerance: does the rather quantititative inheritance of Al tolerance observed in species such as maize and rice necessarily translate into diversity of physiological mechanisms of Al tolerance? It is tempting to speculate that multiple 'Al-tolerance' genes may act by modulating a few sets of physiological mechanisms, which have been fine tuned along the evolutionary history of plant species, providing Al tolerance without undesirable genetic load, thus escaping purifying selection. Clearly, the perspective to find additional functional variation that can lead to transgressive segregation in plant breeding is quite large in the MATE family itself, which furthermore is present as many paralogues that might have acquired divergent functions within some plant species. Therefore, efforts should now be directed to the identification of the molecular determinants of this variation, both within and outside loci encoding organic acid transporter families.

LITERATURE CITED

Brown DG, Swanson JK, Caitilyn A. 2007. Two host-induced *Ralstonia solanacearum* genes, *acra* and *dinF*, encode multidrug efflux pumps and contribute to bacterial wilt virulence. *Applied and Environmental Microbiology* **73**: 2777–2786.

Brown MH, Paulsen IT, Skurray RA. 1999. The multidrug efflux protein NorM is a prototype of a new family of transporters. *Molecular Microbiology* **31**: 393–395.

Chai Y, Lei B, Huang H, Li J, Yin J, Tang Z, Chen L. 2009. *TRANSPARENT TESTA 12* genes from *Brassica napus* and parental species: cloning, evolution, and differential involvement in yellow seed trait. *Molecular Genetics and Genomics* **281**: 109–123.

Debeaujon I, Peeters AJ, Léon-Kloosterziel KM, Koornneef M. 2001. The *TRANSPARENT TESTA12* gene of Arabidopsis encodes a multidrug secondary transporter-like protein required for flavonoid sequestration in vacuoles of the seed coat endothelium. *The Plant Cell* **13**: 853–871.

Diener AC, Gaxiola RA, Fink GR. 2001. Arabidopsis *ALF5*, a multidrug efflux transporter gene family member, confers resistance to toxins. *The Plant Cell* **13**: 1625–1637.

Durrett TP, Gassmann W, Rogers EE. 2007. The FRD3-mediated efflux of citrate into the root vasculature is necessary for efficient iron translocation. *Plant Physiology* **144**: 197–205.

Eckardt NA. 2001. Move it on out with MATEs. *The Plant Cell* **13**: 1477–1480.

Furukawa J, Yamaji N, Wang H, *et al*. 2007. An aluminum-activated citrate transporter in barley. *Plant Cell Physiology* **48**: 1081–1091.

Gomez C, Terrier N, Torregrosa L, *et al*. 2009. Grapevine MATE-type proteins act as vacuolar H+-dependent acylated anthocyanin transporters. *Plant Physiology* **150**: 402–415.

Green LS, Rogers EE. 2004. *FRD3* controls iron localization in Arabidopsis. *Plant Physiology* **136**: 2523–2531.

Hiasa M, Matsumoto T, Komatsu T, Moriyama Y. 2006. Wide variety of locations for rodent MATE1, a transporter protein that mediates the final excretion step for toxic organic cations. *American Journal of Physiology* **291**: 678–686.

Hvorup RN, Winnen B, Chang AB, Jiang Y, Zhou X, Saier MH. 2003. The multidrug/oligosaccharidyl-lipid/polysaccharide (MOP) exporter superfamily. *European Journal of Biochemistry* **270**: 799–813.

Iuchi S, Koyama H, Iuchi A, *et al*. 2007. Zinc finger protein STOP1 is critical for proton tolerance in Arabidopsis and coregulates a key gene in aluminum tolerance. *Proceedings of the National Academy of Sciences of the USA* **104**: 9900–9905.

Kochian LV, Hoekenga OA, Pineros MA. 2004. How do crop plants tolerate acid soils? Mechanisms of aluminum tolerance and phosphorous efficiency. *Annual Review of Plant Biology* **55**: 459–493.

Larsen PB, Geisler MJ, Jones CA, Williams KM, Cancel JD. 2005. ALS3 encodes a phloem-localized ABC transporter-like protein that is required for aluminum tolerance. *The Plant Journal* **41**: 353–363.

Larsen PB, Cancel J, Rounds M, Ochoa V. 2007. Arabidopsis ALS1 encodes a root tip and stele localized half type ABC transporter required for root growth in an aluminum toxic environment. *Planta* **225**: 1447–1458.

Lepiniec L, Debeaujon I, Routaboul J, *et al*. 2006. Genetics and biochemistry of seed flavonoids. *Annual Review of Plant Biology* **57**: 405–430.

Li L, He Z, Pandey GK, Tsuchiya T, Luan S. 2002. Functional cloning and characterization of a plant efflux carrier for multidrug and heavy metal detoxification. *The Journal of Biological Chemistry* **277**: 5360–5368.

Liu J, Magalhaes JV, Shaff J, Kochian LV. 2009. Aluminum-activated citrate and malate transporters from the MATE and ALMT families function independently to confer Arabidopsis aluminum tolerance. *The Plant Journal* **57**: 389–399.

Ma JF. 2007. Syndrome of aluminum toxicity and diversity of aluminum resistance in higher plants. *International Review of Cytology* **264**: 225–252.

Ma JF, Hiradate S. 2000. Form of aluminium for uptake and translocation in buckwheat (*Fagopyrum esculentum* Moench). *Planta* **211**: 355–360.

Ma JF, Hiradate S, Matsumoto H. 1998. High aluminum resistance in buckwheat. II. Oxalic acid detoxifies aluminum internally. *Plant Physiology* **117**: 753–759.

Magalhaes JV, Liu J, Guimarães CT, *et al*. 2007. A gene in the multidrug and toxic compound extrusion (MATE) family confers aluminum tolerance in sorghum. *Nature Genetics* **39**: 1156–1161.

Marinova K, Pourcel L, Weder B, *et al*. 2007. The Arabidopsis MATE TRANSPORTER TT12 acts as a vacuolar flavonoid/H^+-antiporter active in proanthocyanidin-accumulating cells of the seed coat. *The Plant Cell* **19**: 2023–2038.

Maron LG, Piñeros MA, Guimarães CT, *et al*. 2009. Two functionally distinct members of the MATE (multidrug and toxic compound extrusion) family of transporters potentially underlie two major aluminum tolerance QTLs in maize. *The Plant Journal* **61**: 728–740.

Mathews H, Clendennen SK, Caldwell CG, *et al*. 2003. Activation tagging in tomato identifies a transcriptional regulator of anthocyanin biosynthesis, modification, and transport. *The Plant Cell* **15**: 1689–1703.

Morita Y, Kodama K, Shiota S, *et al*. 1998. NorM, a putative multidrug efflux protein, of *Vibrio parahaemolyticus* and its homolog in *Escherichia coli*. *Antimicrobial Agents and Chemotherapy* **42**: 1778–1782.

Morita Y, Kataoka A, Shiota S, Mizushima T, Tsuchiya T. 2000. NorM of *Vibrio parahaemolyticus* is an Na^+-driven multidrug efflux pump. *Journal of Bacteriology* **182**: 6694–6697.

Morita M, Shitan N, Sawada K, *et al*. 2009. Vacuolar transport of nicotine is mediated by a multidrug and toxic compound extrusion (MATE) transporter in *Nicotiana tabacum*. *Proceedings of the National Academy of Sciences of the USA* **106**: 2447–2452.

Moriyama Y, Hiasa M, Matsumoto T, Omote H. 2008. Multidrug and toxic compound extrusion (MATE)-type proteins as anchor transporters for the excretion of metabolic waste products and xenobiotics. *Xenobiotica* **38**: 1107–1118.

Nawrath C, Heck S, Parinthawong N, Métraux J. 2002. EDS5, an essential component of salicylic acid-dependent signaling for disease resistance in Arabidopsis, is a member of the MATE transporter family. *The Plant Cell* **14**: 275–286.

Omote H, Hiasa M, Matsumoto T, Otsuka M, Moriyama Y. 2006. The MATE proteins as fundamental transporters of metabolic and xenobiotic organic cations. *Trends in Pharmacological Sciences* **27**: 587–593.

Otani M, Shitan N, Sakai K, Martinoia E, Sato F, Yazaki K. 2005. Characterization of vacuolar transport of the endogenous alkaloid berberine in *Coptis japonica*. *Plant Physiology* **138**: 1939–1946.

Otsuka M, Matsumoto T, Morimoto R, Arioka S, Omote H, Moriyama Y. 2005. A human transporter protein that mediates the final excretion step for toxic organic cations. *Proceedings of the National Academy of Sciences of the USA* **102**: 17923–17928.

Ryan PR, Raman H, Gupta S, Horst WJ, Delhaize E. 2009. A second mechanism for aluminum resistance in wheat relies on the constitutive efflux of citrate from roots. *Plant Physiology* **149**: 340–351.

Saier MH, Paulsen IT. 2001. Phylogeny of multidrug transporters. *Seminars in Cell and Developmental Biology* **12**: 205–213.

Sasaki T, Yamamoto Y, Ezaki B, *et al*. 2004. A wheat gene encoding an aluminum-activated malate transporter. *The Plant Journal* **37**: 645–653.

Sawaki Y, Iuchi S, Kobayashi Y, *et al*. 2009. STOP1 regulates multiple genes that protect Arabidopsis from proton and aluminum toxicities. *Plant Physiology* **150**: 281–294.

Shen R, Ma JF, Kyo M, Iwashita T. 2002. Compartmentation of aluminium in leaves of an Al-accumulator, *Fagopyrum esculentum* Moench. *Planta* **215**: 394–398.

Shiomi N, Fukuda H, Fukuda Y, Murata K, Kimura A. 1991. Nucleotide sequence and characterization of a gene conferring resistance to ethionine in yeast *Saccharomyces cerevisiae*. *Journal of Fermentation and Bioengineering* **71**: 211–215.

Shoji T, Inai K, Yazaki Y, *et al*. 2009. Multidrug and toxic compound extrusion-type transporters implicated in vacuolar sequestration of nicotine in tobacco roots. *Plant Physiology* **149**: 708–718.

Tanihara Y, Masuda S, Sato T, Katsura T, Ogawa O, Inui K. 2007. Substrate specificity of MATE1 and MATE2-K, human multidrug and toxin extrusions/H^+-organic cation antiporters. *Biochemical Pharmacology* **74**: 359–371.

Tolrà R, Barceló J, Poschenrieder C. 2009. Constitutive and aluminium-induced patterns of phenolic compounds in two maize varieties differing in aluminium tolerance. *Journal of Inorganic Biochemistry* **103**: 1486–1490.

Uhde-Stone C, Liu J, Zinn KE, Allan DL, Vance CP. 2005. Transgenic proteoid roots of white lupin: a vehicle for characterizing and silencing root genes involved in adaptation to P stress. *The Plant Journal* **44**: 840–853.

Yamaji N, Huang CF, Nagao S, *et al*. 2009. A zinc finger transcription factor ART1 regulates multiple genes implicated in aluminum tolerance in rice. *The Plant Cell* **21**: 3339–3349.

Yokosho K, Yamaji N, Ueno D, Mitani N, Ma JF. 2009. OsFRDL1 is a citrate transporter required for efficient translocation of iron in rice. *Plant Physiology* **149**: 297–305.

Zhao J, Dixon RA. 2009. MATE transporters facilitate vacuolar uptake of epicatechin 3′-*O*-glucoside for proanthocyanidin biosynthesis in *Medicago truncatul*a and Arabidopsis. *The Plant Cell* **21**: 2323–2340.

APPENDIX

Two relevant papers were published after this review was accepted: Ryan and Delhaize (*Functional Plant Biology* **37**: 275–284, 2010) discuss evolutionary aspects of aluminium resistance in plants whilst Yokosho *et al.* (*Functional Plant Biology* **37**: 296–303, 2010) describe the isolation of MATE homologues involved with citrate efflux in rye.