



Review

Genetic and molecular mechanisms of aluminum tolerance in plants

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ABSTRACT. Aluminum (Al) toxicity restricts root growth and agricultural yield in acid soils, which constitute approximately 40% of the potentially arable lands worldwide. The two main mechanisms of Al tolerance in plants are internal detoxification of Al and its exclusion from root cells. Genes encoding membrane transporters and accessory transcription factors, as well as *cis*-elements that enhance gene expression, are involved in Al tolerance in plants; thus studies of these genes and accessory factors should be the focus of molecular breeding efforts aimed at improving Al tolerance in crops. In this review, we describe the main genetic and molecular studies that led to the identification and cloning of genes associated with Al tolerance in plants. We include recent findings on the regulation of genes associated with Al tolerance. Understanding the genetic, molecular, and physiological aspects of Al tolerance in plants is important for

generating cultivars adapted to acid soils, thereby contributing to food security worldwide.

Key words: Aluminum; Tolerance; Organic acids; Regulatory factors; QTL

INTRODUCTION

Aluminum (Al) toxicity in acid soils is an important abiotic stress factor that reduces crop yield (Ma et al., 2001). In addition to the extensive distribution of acid soils in tropical and subtropical regions, especially in regions where food supply is more tenuous, agricultural activities can also lead to soil acidification (Ciotta et al., 2002). Under acidic conditions, Al is released from soil minerals in ionic forms such as $\text{Al}(\text{OH})_2^+$, $\text{Al}(\text{OH})_3^0$, and $\text{Al}(\text{H}_2\text{O})_6^{3+}$, with the last species being commonly known as Al^{3+} (Kinraide et al., 1992). Soil with low pH allows for the solubilization and release of Al^{3+} ions into the rhizosphere, causing a highly toxic effect on sensitive plants (Delhaize and Ryan, 1995).

The effect of Al on plant metabolic processes can be observed within minutes after the onset of the stress syndrome, and is followed by secondary effects that occur at later stages (Kochian, 1995). In the cell wall, Al may bind to carboxyl and phosphate groups due to its high affinity for electron donors such as oxygen (Dale and Sutcliffe, 1986), causing structural changes and compromising cell wall expansion (Ma et al., 2004a). Therefore, Al toxicity causes severe damage to root systems, which consequently reduces water and mineral nutrient uptake, thus limiting agricultural yield (Ma et al., 2001; Kochian et al., 2004).

MECHANISMS OF ALUMINUM TOLERANCE

Mechanisms of Al tolerance are classified as those that prevent Al ions from entering the root apical cells (i.e., apoplastic mechanisms) or that detoxify internal Al (i.e., symplastic mechanisms) (Kochian, 1995; Kochian et al., 2004). In symplastic mechanisms, Al enters the cytoplasm and is detoxified once inside the cell by complexation with organic compounds (Kochian, 1995). Several compounds can form stable complexes with Al inside the cell, including organic acids such as citrate, oxalate, malate (Foy, 1988; Taylor, 1988; Ma and Miyasaka, 1998), and proteins (Suhayda and Haug, 1985). Free Al^{3+} or Al complexes with chelating agents can be transported to cell vacuoles, where they are stored without causing toxicity (Kochian et al., 2004).

Apoplastic mechanisms are also known as Al exclusion mechanisms. The following Al exclusion mechanisms have been reported: release of phenolic compounds (Ofei-Manu et al., 2001), mucilage formation (Miyasaka and Hawes, 2001), "pH barrier" resulting from increased pH in the rhizosphere (Degenhardt et al., 1998), and organic acid exudation (Delhaize et al., 1993; Pellet et al., 1995; Sasaki et al., 2004; Magalhaes et al., 2007). Roots of several plant species secrete organic acids in response to Al, which are mediated by membrane transporters, resulting in the formation of non-toxic complexes with the metal. Thus, this mechanism prevents Al from crossing the plasma membrane into the symplast.

Although organic acid exudation is a conserved Al tolerance mechanism being present in different plant species, there are species-specific peculiarities worth noting. The Al-activated

mechanism of malate exudation is well described in wheat (Delhaize et al., 1993; Sasaki et al., 2004), *Arabidopsis* (Hoekenga et al., 2006), *Brassica napus* (Ligaba et al., 2006), and rye (Collins et al., 2008), whereas the mechanism of Al tolerance in maize, soybean, sorghum, and barley involves mainly citrate release (Pellet et al., 1995; Yang et al., 2000; Magalhaes et al., 2007; Furukawa et al., 2007; Maron et al., 2010).

Nevertheless, co-occurrence of different Al tolerance mechanisms has been reported in some species. In maize, root citrate (Piñeros et al., 2002) and oxalate (Kidd et al., 2001) exudation are likely involved in Al tolerance. However, Piñeros et al. (2005) observed a low correlation between citrate exudation and Al tolerance in maize, suggesting that this species has other complementary mechanisms enabling them to tolerate Al. In addition to malate, citrate exudation has also been reported to contribute to Al tolerance in wheat, *Arabidopsis*, and rye (Ryan et al., 2009; Liu et al., 2009; Yokosho et al., 2010). In rice, citrate exudation (Yokosho et al., 2011) as well as symplastic mechanisms are likely to contribute to the extreme Al tolerance in this species (Huang et al., 2009).

ALUMINUM TOLERANCE GENES

The ALMT family

The genetic control of the Al tolerance mechanism based on malate exudation is due to the action of genes encoding aluminum-activated malate transporters in the ALMT family. The first Al tolerance gene to be cloned in plants was designated *TaALMT1*, which encodes a transporter protein involved in malate exudation from root apices and is responsible for Al tolerance in wheat (Sasaki et al., 2004). *TaALMT1* was mapped to chromosome 4DL, co-segregating with a major Al tolerance QTL identified in different wheat populations (Raman et al., 2005; Ma et al., 2005). Based on its location, *TaALMT1* possibly corresponds to the previously mapped Al tolerance loci, *Alt2* (Luo and Dvorák, 1996) and *Alt_{BH}* (Ried and Anderson, 1996).

A large number of *ALMT* members were implicated in malate exudation and Al tolerance in *Arabidopsis* (*AtALMT1*; Hoekenga et al., 2006), rapeseed (*BnALMT1* and *BnALMT2*; Ligaba et al., 2006), rye (*ScALMT1*; Collins et al., 2008), and barley (*HvALMT1*; Gruber et al., 2010). In contrast, *ZmALMT1* (Piñeros et al., 2008) and *ZmALMT2* (Ligaba et al., 2012), two members in the ALMT family, were not found to be associated with maize Al tolerance.

The MATE family

Members of the multidrug and toxic compound extrusion (MATE) family have been associated with several cellular processes, including Al tolerance. Al tolerance in sorghum relies mostly on the *Alt_{SB}* locus, which has a major phenotypic effect and has been mapped to sorghum chromosome 3 (Magalhaes et al., 2004). The *SbMATE* gene mediates Al-activated citrate exudation from root apices and underlies the Al tolerant locus, *Alt_{SB}* (Magalhaes et al., 2007). *SbMATE* expression is induced with time of exposure to Al and is higher in the root apex compared to the rest of the root (Magalhaes et al., 2007). As in sorghum, Al tolerance in barley is related to citrate efflux mediated by *HvAACT1*, which also belongs to the MATE family and is highly expressed in roots of Al-tolerant barley genotypes (Furukawa et al., 2007). QTL mapping in this species has shown that *HvAACT1* is located on chromosome

4H, co-localizing with a major QTL that explains more than 50% of the phenotypic variation in Al-activated citrate exudation (Ma et al., 2004b).

Functional MATE homologs associated with Al tolerance were also identified in *Arabidopsis* (*AtMATE*; Liu et al., 2009), wheat (*TaMATE1*; Ryan et al., 2009), rye (*ScFRDL2*; Yokosho et al., 2010), and rice (*OsFRDL4*; Yokosho et al., 2011). Some of these genes are located near Al tolerance QTL, such as *OsFRDL4*, which co-localizes with a QTL on chromosome 1 that was detected in different studies (Yokosho et al., 2011). A major Al tolerance QTL explaining 49% of the phenotypic variation was mapped to wheat chromosome 3BL (Navakode et al., 2009), which possibly harbors *TaMATE1*. According to the authors, this is supported by the fact that this region in wheat is syntenic to sorghum chromosome 3 and rice chromosome 1, where Al tolerance *MATE* members were located (Navakode et al., 2009).

Two maize MATEs, *ZmMATE1* and *ZmMATE2*, were co-localized with two major Al tolerance QTL on maize chromosomes 6 and 5, respectively (Maron et al., 2010). *ZmMATE1* encodes a transmembrane protein that is highly similar to *SbMATE*, and its overexpression in *Arabidopsis* results in increased citrate exudation as well as higher Al tolerance (Maron et al., 2010). Al tolerance QTL were mapped to this genomic region of chromosome 6 in two other studies using different mapping populations (Sibov et al., 1999; Ninamango-Cárdenas et al., 2003). In contrast, *ZmMATE2* expression, which was not induced by Al, was similar between Al-tolerant and Al-sensitive genotypes (Maron et al., 2010). In addition, association between *ZmMATE2* and citrate exudation has not been found, raising questions to a possible role for *ZmMATE2* in maize Al tolerance.

ATP-binding cassette (ABC) transporter family

In addition to genes encoding organic acid transporters, other genes have been associated with Al tolerance in plants. Two genes encoding ABC transporters, *ALS3* and *ALS1*, were associated with Al tolerance in *Arabidopsis* (Larsen et al., 2005, 2007). *ALS1* is primarily expressed in the root apex and vascular tissues, and *ALS1* is present in vacuolar membranes (Larsen et al., 2007). *ALS3* is expressed in different organs but mainly in leaf hydathodes and phloem, whereas *ALS3* is localized to the plasma membrane (Larsen et al., 2005). Knockout mutants of both genes caused Al hypersensitivity but their overexpression in *Arabidopsis* did not improve Al tolerance. *ALS1* and *ALS3* have been hypothesized to act in the intracellular redistribution of Al, keeping this metal away from sensitive tissues (Larsen et al., 2005, 2007).

In rice, sensitive to aluminum rhizotoxicity genes 1 and 2 (*STAR1* and *STAR2*) were identified and the fact that knocking out either *star1* or *star2* resulted in Al hypersensitivity suggested their function in Al tolerance (Huang et al., 2009). *STAR1* encodes a nucleotide-binding domain, whereas *STAR2* encodes a transmembrane domain of a bacterial-type ABC transporter, which is involved in UDP-glucose transport (Huang et al., 2009). *STAR1* and *STAR2* are primarily expressed in the roots and specifically induced by Al, and the proteins encoded by these genes form a complex that localizes to cytosolic vesicle membranes. Although the mechanism triggered by this transporter is not yet completely understood, the authors suggest that UDP-glucose may be involved in cell wall modifications, reducing the toxic effects of Al (Huang et al., 2009). Recently, a half-size ABC transporter encoded by *OsALS1* was functionally characterized as responsible for Al sequestration into vacuole, which is required for internal detoxification of this metal in rice (Huang et al., 2012).

Nramp family

Recently, the Nramp aluminum transporter 1 (*Nrat1*) was found to be associated with Al tolerance in rice. *Nrat1* belongs to the natural resistance-associated macrophage protein (Nramp) transporter family (Xia et al., 2010). Nramp proteins are conserved in different species and are involved in divalent ion transport (Courville et al., 2006; Xia et al., 2010). *Nrat1* is a transporter located in the plasma membrane of root apical cells, exhibiting transport activity for Al^{3+} , but not for divalent metals or the Al-citrate complex. *Nrat1* expression is induced by Al and is root-specific, occurring in all root cells, except for the epidermis. Knockout lines for *Nrat1* exhibited higher Al sensitivity, higher Al accumulation in the cell wall, and lower Al concentration in root cells in the presence of Al^{3+} (Xia et al., 2010). Such findings led the authors to suggest that *Nrat1* controls intracellular Al^{3+} uptake, with subsequent detoxification via transport and Al accumulation into cell vacuoles, possibly mediated by OsALS1 (Huang et al., 2012).

REGULATION OF ALUMINUM TOLERANCE GENE EXPRESSION

Due to the close relationship between allelic variation for Al tolerance and the expression of Al tolerance genes, efforts are underway to validate the molecular nature of regulatory factors involved in Al tolerance. In *Arabidopsis*, the sensitive to proton rhizotoxicity 1 (*STOP1*) gene was identified, which encodes a transcription factor involved in Al tolerance (Iuchi et al., 2007; Liu et al., 2009; Sawaki et al., 2009). Initially, Iuchi et al. (2007) described a proton-sensitive *Arabidopsis* mutant, where a recessive mutation was detected in a gene encoding a Cys₂-His₂ transcription factor. The *stop1* mutant showed reduced root growth under low pH conditions and under Al toxicity. Interestingly, these phenotypes were associated with inhibited *AtALMT1* gene expression and malate exudation after Al treatment (Iuchi et al., 2007). Microarray analyses of *stop1* indicated that multiple genes possibly involved in Al tolerance are co-regulated by STOP1 (Sawaki et al., 2009). Among those genes is *ALS3* (Larsen et al., 2005), which was repressed in the *stop1* mutant (Sawaki et al., 2009). Additional studies indicated that STOP1 is also necessary for *AtMATE* expression and Al-activated citrate exudation in *Arabidopsis*. Therefore, although both *AtALMT1* and *AtMATE* genes act independently to confer aluminum tolerance in *Arabidopsis*, the STOP1 transcription factor represents a transcriptional link between them (Liu et al., 2009).

The Al resistance transcription factor 1, *ART1*, is a rice homologue of *AtSTOP1* that regulates the expression of several genes related to rice Al tolerance, such as *STAR1* and *STAR2* (Yamaji et al., 2009), *Nrat1* (Xia et al., 2010), *OsFRDL4* (Yokosho et al., 2011) and *OsALS1* (Huang et al., 2012).

Cis-elements are located in non-coding regions along the DNA sequence, near or far from the target gene and influence gene expression (von Korff et al., 2009). *Cis*-acting regulatory sequences, such as polymorphisms within introns, and modified promoter regions, may influence aluminum tolerance in plants.

In sorghum, the coding region of the aluminum tolerance gene, *SbMATE*, was identical between Al-tolerant and Al-sensitive genotypes, with polymorphisms being found in the second intron of *SbMATE*. Furthermore, a tourist-like miniature inverted repeat transposable element (MITE) transposon was detected in the promoter region, and the number of repeats was positively correlated with Al tolerance (Magalhaes et al., 2007). It was then suggested

that the causative mutations underlying aluminum tolerance may have a regulatory nature (Magalhaes et al., 2007).

The *TaALMT1* coding region is conserved between Al-tolerant and Al-sensitive lines (Raman et al., 2005). In turn, a 160-bp transposon and eight SNPs were detected downstream of *ALMT1*, but allelic variation at these loci was not correlated with aluminum tolerance. However, blocks of tandemly repeated sequences that were duplicated or triplicated were found in genomic regions upstream of the *ALMT1* coding region (Sasaki et al., 2006). In general, high *ALMT1* gene expression and Al tolerance were correlated with the number of repeats. Subsequently, transgenic plants containing different *TaALMT1* promoter alleles were shown to enhance gene expression (Ryan et al., 2010).

An important *cis*-element for binding the ART1 transcription factor was identified in the *STAR1* promoter region, which confers aluminum tolerance in rice (Huang et al., 2009; Yamaji et al., 2009; Tsutsui et al., 2011). This element consists of the sequence GGN(T/g/a/C)V(C/A/g)S(C/G), located upstream of the *STAR1* start codon. Moreover, this element was found in the promoter region of 29 of the 31 genes regulated by ART1 (Yamaji et al., 2009; Tsutsui et al., 2011), including *STAR2*, *Nrat1* (Tsutsui et al., 2011) and *OsFRDL4* (Yokosho et al., 2011), which are all involved in rice Al tolerance. In the *STAR2* promoter, two copies of this element were identified, in addition to three copies in the *Nrat1* (Tsutsui et al., 2011) promoter region.

More recently, a distinct mechanism for regulating *HvAACT1* expression was presented in barley (Fujii et al., 2012). An insertion of 1-kb sequence at 6 kb upstream from the *HvAACT1* coding region added multiple transcriptional start sites, enhancing this gene expression in the root tips. The modified *HvAACT1* expression pattern resulted in a superior Al-induced citrate exudation that consequently improved Al tolerance in barley (Fujii et al., 2012).

CONCLUSION

Plants have developed several mechanisms to overcome the limitations imposed by Al toxicity. Despite a prevalence of mechanisms involving organic acid exudation, symplastic mechanisms also play a role in Al tolerance in plants. In some species, Al tolerance is a genetically complex trait, where different tolerance mechanisms coexist. The involvement of multiple mechanisms is apparently independent of the level of tolerance intrinsic to each species, occurring in both comparatively Al-sensitive species, such as *Arabidopsis*, and highly Al-tolerant species, such as rice. Molecular and genetic studies have contributed to the identification of genes associated with Al tolerance. Those genes include membrane transporters of the ALMT, MATE, and ABC families, and functional homologs of these transporter genes are found in different species. Transcriptional factors and *cis*-elements are highly involved in the expression of Al tolerance genes. Integrating information about QTL, genes, and mechanisms involved in Al tolerance allows for a broad understanding of this trait across different plant species. Pyramiding of these genes and tolerance mechanisms by marker-assisted introgression of superior alleles or via genetic transformation may significantly contribute to the development of highly Al tolerant cultivars by molecular breeding, which should contribute to crop production on acid soils.

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