The Molecular Physiology and Regulation of Aluminum Resistance in Higher Plants

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Abstract Plants have evolved a variety of aluminum (Al)-resistance mechanisms that are regulated by complex biological systems. Two distinct categories of Al resistance were proposed in the late 1980s, namely "exclusion" of Al from the symplasm and "internal tolerance." Exclusion mechanisms reduce the amount of rhizotoxic Al (Al^{3+}) in the symplasm of cells and internal tolerance mechanisms reduce Al toxicity, and the resulting damage occurs once Al has entered the cytosol. Since these concepts were introduced, many studies have identified physiological and genetic mechanisms of Al resistance that provide support for "exclusion" and "internal tolerance" at the molecular level. Excretion of organic anions (OA) from root cells, which detoxify Al by chelation, appears to be the most common mechanism of Al exclusion in plants. In addition, modification of the chemical properties of the plasma membrane and cell wall contribute to a reduction of Al rhizotoxicity in the root tips. Sequestration of Al in the vacuole, translocation of Al to the shoot, and enhanced capacity to cope with Al-inducible reactive oxygen species are important mechanisms of internal Al tolerance. Various genes that control these traits, such as genes encoding OA transporters, have been identified in plants. Studies of the transcriptional regulation of these genes by STOP1/ART1-type zinc finger transcription factors show that multiple Al-resistance genes are likely co-regulated by the same signal transduction pathway in different plant species. In addition, regulation of Al-resistance mechanisms is coordinated with resistance to other stress factors associated with the acid soil syndrome.

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1 Molecular Physiology of Al^{3+} Rhizotoxicity

Many crops grow poorly on acid soils due to acid soil syndrome. This syndrome consists of multiple stress factors, including toxicities of aluminum (Al^{3+}), manganese (Mn^{2+}), and protons (H^+) and deficiencies of calcium (Ca^{2+}) and phosphates (PO_4^{2-}; Taylor 1991; Kochian et al. 2004). While these stress factors induce complex stress conditions, Al^{3+} rhizotoxicity is considered to be the most harmful in terms of yield loss, particularly under conditions of drought stress. If a plant is incapable of developing an adequate root system as a result of Al^{3+} rhizotoxicity, it becomes susceptible to drought because it cannot access water in the subsoil (Foy 1992; Lynch and Wojciechowski 2015).

Molecular mechanisms of Al rhizotoxicity have been reported in several studies making use of the model plant, Arabidopsis (*Arabidopsis thaliana*). The harmful effects of Al^{3+} appear at growing root tips because Al^{3+} disturbs essential processes involved in cell division, elongation (Matsumoto 2000), and genotoxicity (Nezames et al. 2012b). A study with corn demonstrated that cells in the distal transition zone (DTZ), where cells are preparing to undergo elongation, is one of the most sensitive parts of the root to Al^{3+} toxicity (Sivaguru and Horst 1998). One of the mechanisms that regulates this process has been clarified by a molecular physiological study of Arabidopsis. By combining reverse genetics of Al-inducible genes and characterization of ethylene signaling mutants, Yang et al. (2014) concluded that inhibition of root growth is driven by a localized increase in IAA biosynthesis in the DTZ, which in turn is regulated by ethylene signaling. However, a loss of function mutation in the cell cycle checkpoint regulator *TANMEI* (*ATAXIA TELANGIECTASIA-MUTATED AND RAD3-RELATED*) conferred Al resistance (Nezames et al. 2012b), suggesting that Al^{3+} is also genotoxic and targets cell division in the root tip.

The bulk of Al in neutral and basic soils exists in nontoxic forms such as Al oxide and aluminosilicates. In acid soils, Al is mobilized as rhizotoxic Al^{3+}, the most toxic of the monomeric ions (Kinraide 2003). Aluminum toxicity in acid soils can be amended by liming, which neutralizes soil acidity (Kinraide 1998). Aluminum in soil solution is controlled at sufficiently safe levels for sensitive root cells if the soil pH is >5.5, but overtreatment with liming may induce harmful effects through alkalinity. Application of gypsum ($CaSO_4$) to partially neutralized soil (e.g., pH 5.0–5.5) eliminates the harmful effects of Al in the soil. $CaSO_4$ is a neutral salt (i.e., no neutralization of acidity) that can increase Ca concentrations in the soil solution more effectively than $CaCO_3$ (Sumner et al. 1986). A molecular physiological study of Arabidopsis provided experimental evidence that explains the complexity of Al rhizotoxicity in acid soils, including the ameliorative effects of $CaSO_4$ (Kobayashi et al. 2013b; Fig. 1).

Electrostatic studies have modeled the rhizotoxicity of Al for growing roots of wheat and other plant species. These studies predicted that rhizotoxicity is determined by Al^{3+} activity at the plasma membrane (PM) surface ($\{Al^{3+}\}_{PM}$), as opposed to Al^{3+} activity in the bulk-phase solution ($\{Al^{3+}\}_{bulk}$; Kinraide 1994,

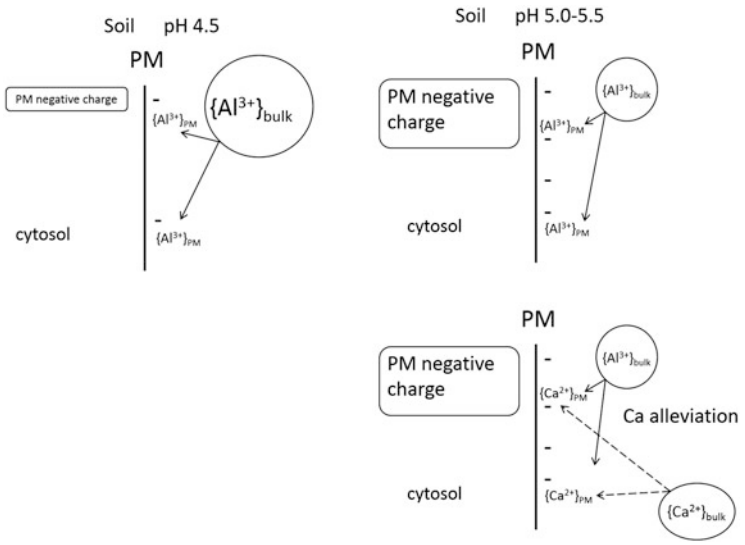

Fig. 1 Mechanism of Al rhizotoxicity and Ca alleviation in weakly acidic soils. Aluminum rhizotoxicity is determined by $\{Al^{3+}\}$ at the plasma membrane (PM) surface ($\{Al^{3+}\}_{PM}$). At pH > 5.0, $\{Al^{3+}\}$ in the bulk-phase soil solution decreases compared with that at pH 4.5. By contrast, the negative charge of weakly acidic ligands (phospholipids) increases at pH > 5.0 compared with lower pH. Through the balance of these two factors, $\{Al^{3+}\}_{PM}$ is maintained at pH 5.0–5.5 and shows rhizotoxicity. The toxicity can be efficiently negated by increasing $\{Ca^{2+}\}_{PM}$ by application of a soluble Ca fertilizer such as gypsum (see Kobayashi et al. 2013b)

1998). The activity of $\{Al^{3+}\}_{PM}$, the Al^{3+} attracted to the PM surface, is determined by both the $\{Al^{3+}\}_{bulk}$ and the electronegativity at the PM surface. In the pH range of 5.0–5.5, $\{Al^{3+}\}_{bulk}$ is decreased compared with that at lower pH (e.g., pH 4.5). In contrast, the electronegativity of the PM increases owing to dissociation of H^+ from weakly acidic phospholipids. Within this pH range, Al-sensitive mutants of Arabidopsis show Al-induced inhibition of growth that completely fits predictions of the electrostatic model. Application of a sufficient amount of Ca^{2+} removes $\{Al^{3+}\}_{PM}$ by masking negative ligands on the PM surface by increasing $\{Ca^{2+}\}_{PM}$ (Ryan et al. 1993). This may account for the alleviative effects of gypsum on Al rhizotoxicity in partially neutralized soils. In fact, an Arabidopsis mutant (the double mutant of *phosphatidate phosphohydrolase 1* and *2*) that has a greater negative charge on the PM surface, because of its inability to convert phospholipids to electrically neutral lipids (Eastmond et al. 2010), is more susceptible to Al rhizotoxicity than the wild type in partially neutralized acid soil. Growth of *pah1pah2* is recovered by application of gypsum (Kobayashi et al. 2013b).

2 Molecular Mechanisms of Al Resistance

Two distinct categories of Al resistance were proposed in the late 1980s, namely "exclusion" of Al from the symplasm and "internal tolerance" (Taylor 1987, 1988, 1991). These categories broadly reflected monographs by Levitt (1980) that categorized resistance mechanisms as either "avoidance" mechanisms or "tolerance" mechanisms. In the context of Al, exclusion mechanisms were defined as those that reduce the amount of rhizotoxic Al (Al^{3+}) in the symplasm of cells. Internal tolerance mechanisms were defined as those that reduce Al toxicity and the resulting damage that occurs once Al has entered the cytosol. A more modern view might be that exclusion mechanisms are those that reduce the amount of rhizotoxic Al (Al^{3+}) in the symplasm and at sensitive sites within the apoplasm (e.g., the plasma membrane surface), while tolerance mechanisms reduce Al toxicity and the resulting damage that occurs once Al has access to these sensitive sites.

Since these concepts were introduced, many studies have identified physiological and genetic mechanisms of Al resistance that provide support for "exclusion" and "tolerance" at the molecular level, including a series of studies with Arabidopsis and rice that have identified molecular mechanisms of Al resistance that protect sensitive root tips from Al toxicity. In this section, we review our current understanding of molecular mechanisms of organic anion (OA) excretion and internal Al tolerance.

2.1 Molecular Mechanisms of Organic Anion Excretion from Roots

Excretion of OA from roots plays a critical role in protection of root tips from Al rhizotoxicity in many plant species (Kochian et al. 2004). Organic anions such as citrate, malate, and oxalate can detoxify Al in the rhizosphere by chelation, since chelated forms are less toxic than Al^{3+}. Differences in both the form and amount of OAs that are excreted determine varietal differences in resistance to Al among many plant species (Ma et al. 1998; Zheng et al. 1998; Wenzl et al. 2001; Kobayashi et al. 2005). The amount of OAs excreted from roots is usually not sufficient to detoxify $\{Al^{3+}\}_{bulk}$, but it may protect sensitive root tips by reducing $\{Al^{3+}\}_{PM}$. A modeling study suggested that excretion of OAs is likely optimized to avoid unnecessary carbon loss, while still reducing Al uptake across the PM (Kinraide et al. 2005). This process is controlled by transcriptional regulation of transport genes that mediate OA excretion and activation of OA transporters by Al.

Genes that encode OA transporters capable of mediating Al resistance have been isolated from a variety of plant species during the last decade. A gene for a malate transporter involved in Al-induced malate excretion was first isolated from wheat (Sasaki et al. 2004). This gene, *TaALMT1* (*Triticum aestivum ALUMINUM ACTIVATED MALATE TRANSPORTER1*), encodes a malate transporter localized at the

plasma membrane, which is activated by exogenous addition of Al. Similar patterns of Al-induced excretion have been observed for citrate excretion. Genes that encode the citrate-transporting MULTIDRUG AND TOXIC COMPOUNDS EXTRUSION (MATE) transporters were first isolated from barley (Furukawa et al. 2007) and sorghum (Magalhaes et al. 2007). Functional orthologous genes have been isolated from Arabidopsis (Liu et al. 2009), various crop species (Liu et al. 2013; Yokosho et al. 2011), and woody plant species (Sawaki et al. 2013). The expression pattern of specific OA transport genes determines a plant's overall pattern of OA excretion. For example, the expression level of the *ALMT1* from Arabidopsis (*AtALMT1*) is higher than that of *AtMATE*, which explains why it excretes a larger amount of malate than citrate (Sawaki et al. 2009).

Aluminum-inducible excretion of OAs is regulated at both the transcriptional and posttranslational levels. Although *TaALMT1* was reported to be a constitutively expressed gene (Sasaki et al. 2004), expression of orthologues of both *ALMT1* and *MATE* in a variety of plant species is Al-inducible. In Arabidopsis, pharmacological studies using inhibitors of protein phosphatases and kinases suggest that Al-inducible expression of *AtALMT1* involves protein phosphorylation/dephosphorylation (Kobayashi et al. 2007). A protein kinase inhibitor (staurosporine) and a protein phosphatase inhibitor (calyculin A) both inhibit Al-induced expression of *AtALMT1* and a citrate-transporting *MATE* in eucalyptus (Sawaki et al. 2013). Specific protein kinases and protein phosphatases involved in this response are yet to be identified, but these results strongly suggest that protein phosphorylation is involved in the activation of OA transporter proteins by Al.

Studies of *Ta*ALMT1 demonstrate that exogenous Al can trigger malate-transport activity (Sasaki et al. 2004). When *TaALMT1* is expressed in *Xenopous* oocytes, addition of Al to the incubation solution activates malate transport. Substitution of negatively charged amino acids of ALMT1 that are conserved among a variety of species inactivates transport activity, suggesting that binding of Al^{3+} to specific negatively charged amino acids in the protein is essential for malate excretion (Sasaki et al. 2014). In addition, studies with Arabidopsis suggest that protein phosphorylation plays a critical role in Al activation of malate transport by ALMT1 (Kobayashi et al. 2007). Normally, Al-induced malate excretion abruptly ceases if Al is removed from the incubation solution. However, addition of a protein phosphatase inhibitor results in continued malate excretion when plants are moved to an Al-free solution. This suggests that protein dephosphorylation is required for the inactivation of *At*ALMT1. In addition, mutation of several amino acids in putative target sites for protein phosphorylation altered the Al activation of *Ta*ALMT1 (Ligaba et al. 2009). These reports suggest that Al activation of ALMT1 for malate excretion is regulated in a complex manner that involves chemical (i.e., Al binding) and biological (i.e., protein phosphorylation) processes.

In Arabidopsis, Al-induced expression of *AtALMT1* shows time- and dose-dependent responses across a wide dynamic range (e.g., 100 times that of control). This suggests that expression of *AtALMT1* is regulated by multiple transcription factors (Kobayashi et al. 2013a; Tokizawa et al. 2015). In fact, a series of transcription factors have now been identified (Tokizawa et al. 2015) (Fig. 2). A zinc finger

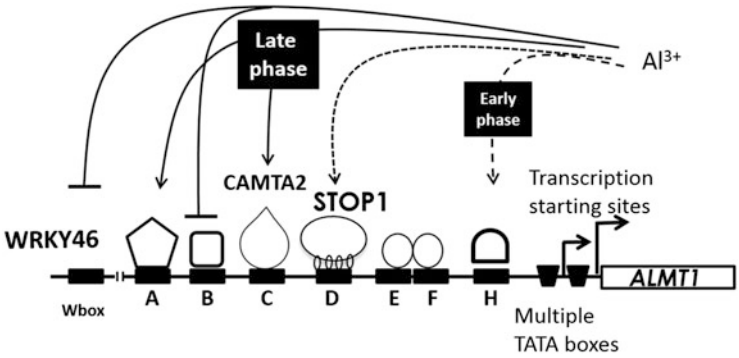

Fig. 2 Promoter structure and transcription factors controlling *AtALMT1* for Al-inducible gene expression. STOP1 transcription factors are critical for *AtALMT1* expression and are involved in the early response to Al. CAMTA2 (a transcription activator) and WRKY46 (a transcription repressor) regulate the late phase of the Al response. Expression of these genes is suppressed (*WRKY46*) and induced (*CAMTA2*) by Al. Multiple transcription starting sites are regulated by corresponding TATA boxes

protein SENSITIVE TO PROTON RHIZOTOXICITY1 (STOP1) is essential for induction of *AtALMT1* expression (Iuchi et al. 2007, 2008). A WRKY-DOMAIN CONTAINING TRANSCRIPTION FACTOR 46 (WRKY46) functions as a transcriptional repressor (Ding et al. 2013), and a CALMODULIN-BINDING TRANSCRIPTION ACTIVATOR2 (CAMTA2) functions as a transcriptional activator (Tokizawa et al. 2015). Expression of *WRKY46* is repressed by Al, while *CAMTA2* expression is induced. The *AtALMT1* promoter possesses *cis*-elements that interact with unidentified repressors and activators that determine its specific expression in the root tip. In addition, the *AtALMT1* promoter carries multiple TATA boxes, which is a common characteristic of stress-responsive genes that show a wide-dynamic range of expression (Yamamoto et al. 2011; Fig. 2). Such activation is highly sensitive to $\{Al^{3+}\}_{PM}$. For example, *AtALMT1* expression is induced at a lower $\{Al^{3+}\}_{PM}$ than that required to induce toxicity in the *Atalmt1* mutant, which is hypersensitive to Al. This finding suggests that the Al-sensing system for activation of *AtALMT1* is sufficiently sensitive to provide protection from Al toxicity at physiological relevant concentrations (Kobayashi et al. 2013b).

Excretion of OAs is likely linked to the biosynthesis and metabolism of OAs. It has been shown that overexpression of citrate synthase confers Al resistance by enhancing citrate excretion (de la Fuente et al. 1997; Anoop et al. 2003). Overexpression also improves phosphate acquisition from sparingly soluble Al-phosphate present in soil (Koyama et al. 1999, 2000). Immobilization of phosphate by Al is a common problem in acidic soil, and thus this approach should be useful for molecular breeding of acidic soil-tolerant varieties that show both Al resistance and efficient utilization of P from Al-phosphate. Other metabolic engineering procedures, such as overexpression of phospho*enol*pyruvate carboxylase, have been also reported in various plant species (Trejo-Téllez et al. 2010). However, the interaction of OA metabolism and regulation of OA transporters remains unclear.

2.2 *Internal Al Tolerance: Sequestration, Efflux of Al, and Adaptation to Al-Induced ROS Damage*

Notwithstanding its polyvalent nature, Al quickly enters the cytoplasm after Al is attracted to the PM surface. A study using the ^{26}Al isotope to measure short-term Al influx in *Chara corallina* determined that Al can enter the cytoplasm within a few minutes (Taylor et al. 2000). Subsequently, Al present in the cytoplasm was sequestrated into the vacuole. Recently, a vacuolar Al transporter and a plasma membrane Al transporter were identified as key components of Al resistance in rice. Aluminum-resistant cultivars showed a higher expression level of *NRAMP ALUMINUM TRANSPORTER1* (*NRAT1*) than sensitive cultivars (Li et al. 2014). Enhanced uptake of Al is ultimately linked to higher sequestration in the vacuole and may reduce the amount of Al at the PM surface and/or cell wall (Li et al. 2014). These results suggest that sequestration of Al into the vacuole is an important strategy for Al resistance. A homologue of ALUMINUM SENSITIVE 1 (ALS1) in rice (*Os*ALS1; Huang et al. 2012) has been characterized as a vacuolar Al transporter. Aluminum uptake by NRAT1 and sequestration into the vacuole by *Os*ALS1 might be coordinately regulated. The vacuolar sequestration of Al appears to be dependent on the activity of the vacuolar H^+-ATPase. Dysfunction of the vacuolar H^+-ATPase in yeast results in an Al-hypersensitive phenotype (Hamilton et al. 2001a, b).

Aluminum efflux (export) from the cytoplasm is one mechanism of internal Al tolerance. An Al-sensitive mutant of *Arabidopsis*, *aluminum sensitive 3* (*als3*), accumulates Al in the root tips and decreases amounts of Al in the shoots (Larsen et al. 2005). These results suggest that ALS3 is involved in translocation of Al from roots to shoots. *ALS3* encodes a half-type ABC transporter (bacterial type), and the homologue *SENSITIVE TO ALUMINUM RHIZOTOXICITY2* (*STAR2*) has been isolated by positional cloning of a rice Al-sensitive mutant (Huang et al. 2009). In rice, the STAR1–STAR2 complex transports UDP-glucose rather than Al. This suggests that ALS3-like proteins transport UDP-glucose and are associated with Al efflux from the cell by a currently unknown mechanism (Fig. 3).

Treatment with Al triggers production of free radicals, and a subsequent antioxidant response is induced in a wide range of plant species. Production of reactive oxygen species (ROS) by Al is seemingly induced in a complex manner. In tobacco BY-2 cells, Al induces ROS production, which in turn initiates membrane lipid peroxidation. The harmful effects of Al are sharply enhanced in the presence of Fe^{2+} (Yamamoto et al. 1997, 2002). This suggests that production of free radicals might be enhanced biochemically as a result of Fenton-like reaction mechanisms. This is supported by studies of solution chemistry in which a pro-oxidant activity of Al is observed where Al activates the Fenton reaction in conjunction with Fe (Mujika et al. 2011; Ruipérez et al. 2012). In addition, Al treatment induces a series of physiological events that increase ROS production. For example, Al treatment transiently increases the Ca^{2+} concentration in the cytosol (Bhuja et al. 2004), and it can activate NADPH oxidase of the PM, resulting in production

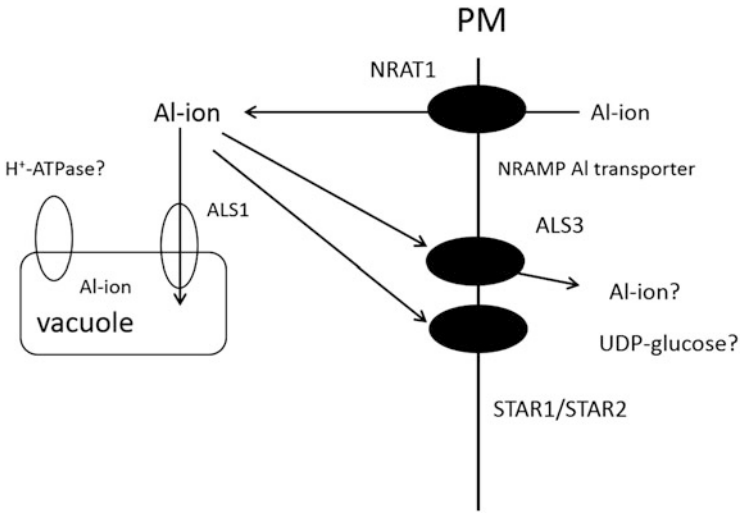

Fig. 3 Sequestration and export of Al from the cytosol by multiple transporters. An NRAMP-type Al transporter (NRAT1) transports Al and possibly maintains $\{Al^{3+}\}_{PM}$ at a low level. In the cytosol, ALS1 and other vacuolar transporters sequester Al into the vacuole. Research on Arabidopsis suggests that ALS3 exports Al from the cytoplasm, but the rice homologue STAR2 (by interaction with STAR1) is reported to transport UDP-glucose, but not Al

of superoxide radicals ($O_2^{\bullet -}$) (Sagi and Fluhr 2001). Histochemical analysis of transgenic Arabidopsis expressing a gene for a pH-sensitive green fluorescent protein showed that Al acidifies the cytosol (Moseyko and Feldman 2001) and disturbs redox homeostasis through inactivation of the reduction capacity of thiol reductants at pH < 7.0. Taken together, these findings indicate that Al induces ROS production in the cytoplasm after its attraction to the PM.

Plant cells express a variety of genes that encode ROS-scavenging enzymes in response to treatment with Al (Richards et al. 1998). Research on transgenic plants reveals that overexpression of these ROS-responsive genes confers Al resistance. For example, Ezaki et al. (2000) demonstrated that ectopic expression of *NtPox* (tobacco peroxidase) and *parB* (tobacco glutathione *S*-transferase) confers Al resistance in transgenic Arabidopsis. Basu et al. (2001) reported that overexpression of *MnSOD* (superoxide dismutase) confers Al resistance in *Brassica napus*. It has been suggested that enhanced transcription of genes for ROS-scavenging enzymes is involved in Al resistance (Basu et al. 2001). By analogy to work yeast, other components of the ROS-scavenging system such as phospholipid hydroperoxide glutathione peroxidases (PHGPX) and UREidosuccinate transport (URE2) might also play a role in mediating resistance (Basu et al. 2004) (Fig. 4).

Transcriptome analyses indicate that many metabolic pathways are altered in response to treatment with Al, including the nitrogen and sulfur assimilation pathways. These responses suggest that metabolic reprogramming might play an

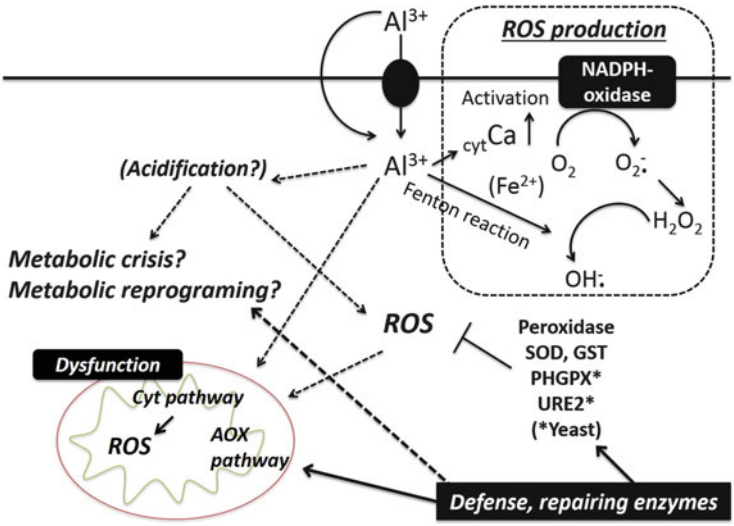

Fig. 4 Aluminum-induced reactive oxygen species (ROS) stress. Aluminum increases cytosolic Ca concentrations, which triggers activation of NADP-oxidase. This process produces H_2O_2, which then amplifies ROS production by a Fenton-like reaction. Aluminum is known to acidify the cytosol, and acidification is known to be a factor that induces metabolic crisis. Aluminum also shifts mitochondrial respiration to an alternative pathway. Overexpression of genes for peroxidase, alternative oxidase (AOX), and other enzymes confers Al resistance in some plant species and yeast

important role in adaptation to Al toxicity. Metabolic reprogramming helps to detoxify ROS and maintain the cellular energy status under stress conditions (Baena-González et al. 2007). Overexpression of a plastid-localized malate dehydrogenase, which performs roles in malate metabolism and redox homeostasis, confers Al resistance in alfalfa (Tesfaye et al. 2001). Recently, an Al-sensitive mutant of Arabidopsis that synthesizes lower amounts of polyamines (including spermine) than the wild type has been isolated (Nezames et al. 2012a). Polyamine synthesis plays roles in adaptation to ROS stress in a wide range of organisms (Alcázar et al. 2010).

Aluminum-induced ROS production results in mitochondrial dysfunction, which is a critical event in the inhibition of cell growth in tobacco cell lines (Yamamoto et al. 1997). More recent studies have shown that ROS signaling activates the alternative oxidase (AOX) pathway, which has a protective role in the stress responses in plants (Panda et al. 2008). The contribution of *AOX* upregulation to Al resistance is further supported by the finding that tobacco cells overexpressing *AOX* show improved resistance to Al (Panda et al. 2013). Upregulation of genes encoding components of ROS scavenging pathways plays a role in other mechanisms active in Al resistance, in particular recovery from oxidative damage. Altogether, we infer that alteration of metabolic pathways involving metabolic reprogramming is involved in ROS-mediated transcriptomic adaptation.

3 The STOP1/ART1 System Controls Expression of Al-Resistance Genes

The zinc finger transcription factor SENSITIVE TO PROTON RHIZOTOXICITY1 (STOP1) was identified by positional cloning of an H^+-sensitive mutant of Arabidopsis (Iuchi et al. 2007). Root growth of the *stop1* mutant was inhibited by low pH (H^+-rhizotoxicity). Interestingly, the mutant also showed hypersensitivity to Al. Furthermore, *AtALMT1* expression was completely suppressed. Further investigation showed that multiple Al-resistance and H^+-resistance genes are co-regulated by the same regulatory system (Fig. 5). For example, the major Al-resistance genes *ALS3* and *AtMATE* were co-repressed in the *stop1* mutant (Sawaki et al. 2009). A rice orthologue of *STOP1*, *ALUMINUM-RESISTANCE TRANSCRIPTION FACTOR1* (*ART1*), was also identified by positional cloning of an Al-sensitive mutant (Yamaji et al. 2009). The *art1* mutant shows repression of homologues of *ALS3* (rice; *STAR2*) and *AtMATE* (rice; *OsFRDL4*). In addition, a magnesium transporter (Chen et al. 2012) and a plasma-membrane-localized cysteine-rich peptide (Xia et al. 2013) are critical for Al resistance in rice, and their expression is regulated by the ART1 transcription factor.

It has been suggested that the STOP1/ART1 pathway (Fig. 5) is shared by a wide range of plant species. This suggestion has been further analyzed in various plant

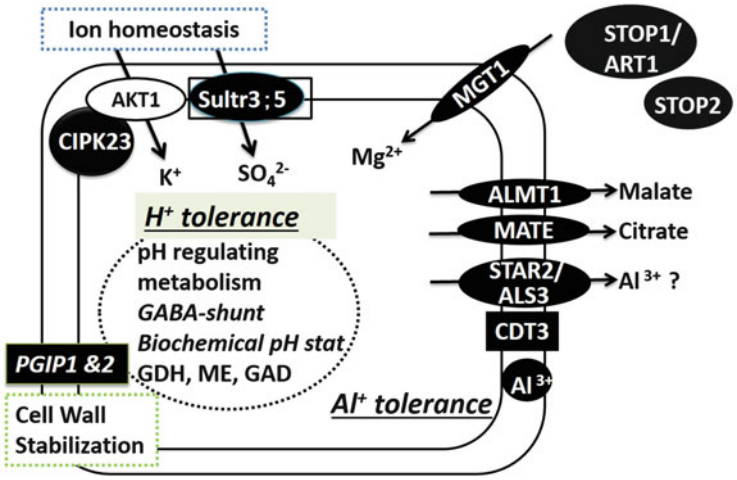

Fig. 5 STOP1/ART1 regulatory genes involved in resistance to Al and proton toxicity. Functional analyses of STOP1 in Arabidopsis and ART1 in rice show that multiple genes controlling Al and proton resistance are coordinately regulated by STOP1/ART1 zinc finger transcription factors. MGT1, magnesium transporter 1; ALMT, aluminum-activated malate transporter; MATE, citrate-transporting MATE; STAR2/ALS3, aluminum-sensitive 3 protein; GDH, glutamate dehydrogenase; ME, malic enzyme; GAD, gamma butyric acid decarboxylase; PGIP, polygalacturonase inhibitor protein; AKT1, Arabidopsis K^+-transporter; CIPK23, CBL-interacting protein kinases (regulator of AKT1); CDT3 (Cys rich small protein in rice)

species, including woody plants [e.g., *Eucalyptus*, Sawaki et al. (2014)], monocots [e.g., wheat, Garcia-Oliveira et al. (2013), and bryophytes (Ohyama et al. (2013)]. Knockdown of the *STOP1* orthologue in the moss *Physcomitrella patens* suppresses Al resistance (Ohyama et al. 2013). These findings indicate that the STOP1/ART1 system may be ubiquitous among land plant species.

Reverse genetics of STOP1 orthologues provides a powerful approach to uncover molecular mechanisms of Al resistance in plant species. Knockdown of the STOP1 orthologue in tobacco results in an Al-sensitive phenotype. Aluminum-responsive citrate excretion plays a critical role in Al resistance in this plant species and is transcriptionally regulated by a citrate-transporting MATE that is regulated by the STOP1 orthologue. A similar approach may be useful to clarify unidentified Al-resistance mechanisms at the molecular level. For example, knockdown in buckwheat and tea plants may enable identification of the gene encoding the oxalate transporter that contributes strongly to Al resistance of these plants (Zheng et al. 1998).

The STOP1/ART1 system involves other transcription factors in the Al signaling process (Fig. 5). Arabidopsis carries a unique homologue of STOP1, namely STOP2, whose expression is regulated by STOP1 (Kobayashi et al. 2013c). Functional analyses show that STOP2 cannot activate transcription of *AtALMT1*, but can activate *AtMATE* and ALS3. ABSCISIC ACID, STRESS AND RIPENING 5 (ASR5) has been identified in rice and coordinately regulates expression of *STAR1* with ART1 (Arenhart et al. 2014). Interestingly, a genome-wide BLAST search indicates that Arabidopsis does not possess an *ASR5* orthologue, but target *cis*-elements that have been coordinately identified in the promoter of *AtALMT1* with the *cis*-element of STOP1 (Tokizawa et al. 2015). In wheat, the same combination is conserved in the promoter of *TaALMT1*, which suggests that a series of orthologous transcription factors coordinately regulate Al-resistance genes in various plant species.

A recent study utilizing a systems biology approach clarified that in the *stop1* mutant, many genes encoding proteins that contribute to H^+ resistance are suppressed (Sawaki et al. 2009). For example, the regulatory proteins of the major K^+-transporter *ARABIDOPSIS K-TRANSPORTER1* (*AKT1*) and sulfate transporter *SULFATE TRANSPORTER 3.1* (*Surtr 3.1*), which play an important role in ion homeostasis, are repressed in the *stop1* mutant. As another example, genes encoding enzymes that belong to pH-regulatory pathways such as the biochemical pH-stat and GABA (γ-amino butyric acid shunt)-shunt (Bouche and Fromm 2004) are repressed in the *stop1* mutant. In addition, two genes that are involved in stabilization of the cell wall pectic-polysaccharide network, *POLYGALACTURONASE INHIBITING PROTEIN 1* and *2* (*PGIP1* and *PGIP2*; Spadoni et al. 2006), are also repressed in the *stop1* mutant. These genes are controlled by STOP2, and the growing root tips of *pgip1* and *pgip2* show enhanced cellular damage in low-pH solution that is associated with the stability of the pectin network. Co-regulation of Al- and H^+-resistance genes by the same transduction pathway is reasonable because H^+ rhizotoxicity is apparent in naturally acidic soils in which Al becomes soluble.

In Arabidopsis, a variety of Al-resistance genes are also inducible by H^+. We suggest that Al^{3+} and H^+ generate an identical signal, although the sensory mechanisms (e.g., the receptor protein) of each stressor remain unknown. However, Al-resistance genes play pleiotropic roles in other stress responses. For example, malate excreted via the functioning of *At*ALMT1 recruits beneficial rhizobacteria to the root surface. The recruitment of rhizobacteria may activate systemic-induced resistance. Infection of aerial tissues by pathogenic bacteria or the FLG22 peptide (a conserved peptide pattern in bacterial flagella) induced expression of *AtALMT1* in roots (Kobayashi et al. 2013a). These results reflect the dual function of AtALMT1 in Al resistance and plant immune responses. Similarly complex regulation has been observed for ALMT1 in soybean. Transcription of that gene is activated by Al- and P deficiency (Liang et al. 2013). This finding is consistent with the proposed role of OA excretion in increased P acquisition.

Membrane-binding proteins, such as receptors or other proteins that can induce signals (e.g., changes in pH and Ca^{2+} concentration in the cytoplasm, H_2O_2 production), may be involved in the initial step of Al signaling. Further research is needed to identify the molecular mechanisms underlying these processes. In addition, longer exposure to Al can initiate ABA signaling because depressed root growth can lead to water deficiency in aerial tissues, thereby inducing ABA signaling (Zhang et al. 2006). As well, longer exposure to Al can initiate IAA accumulation as a result of ethylene-mediated signaling at the root tips by Al (Yang et al. 2014). ROS-mediated signals and ROS-induced disruption of respiration and metabolic pathways may also trigger complex signals. For example, specific metabolites such as Fe–citrate can activate transcription of several genes involved in primary metabolism (Finkemeier et al. 2013).

As described above, many genes and proteins that are directly involved in mediating resistance to Al and genes and proteins involved in regulation of resistance have been reported in last decade. These findings have enriched our knowledge of the molecular basis of Al resistance in a wide variety of plants. Collectively, these studies suggest that various resistance mechanisms are coordinately regulated in a complex manner. Further research is required to elucidate the complex signaling systems that mediate Al resistance and the mechanisms to repair Al-induced damage in plants.

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