MicroRNAs as regulators in plant metal toxicity response

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MicroRNAs (miRNAs) have been recognized as key regulators in a broad range of biological processes including metabolism, development and abiotic stress responses (Arnaiz-Villena et al., 2010; Rellán-Álvarez et al., 2006; Lequeux et al., 2002). Plant responses to metal toxicity include the synthesis of metal-binding proteins and phytochelatins. For instance, the expression of metallothionein genes in transgenic tobacco expressing a cadmium-resistant transgene was induced upon Cd stress (Kim et al., 2002). The expression of metallothionein gene in transgenic tobacco expressing a cadmium-resistant transgene was induced upon Cd stress (Kim et al., 2002).

Metal toxicity stress triggers the accumulation of ROS (reactive oxygen species), unbalancing the activity of antioxidative enzymes that are up-regulated by this stress (Romero-Puertas et al., 2007). Oxidative stress leads to damage of lipids, proteins, and DNA (Schützendübel and Polle, 2002). Metal toxicity stress involves the accumulation of ROS (reactive oxygen species), unbalancing the activity of antioxidative enzymes that are up-regulated by this stress (Romero-Puertas et al., 2007). Oxidative stress leads to damage of lipids, proteins, and DNA (Schützendübel and Polle, 2002).

Metal toxicity is a major stress affecting crop production. This includes metals that are essential for plants (copper, iron, zinc, manganese), and non-essential metals (cadmium, aluminum, cobalt, mercury). A primary common effect of high concentrations of metal such as copper, cadmium, or mercury is root growth inhibition. Metal toxicity triggers the accumulation of reactive oxygen species leading to damage of lipids, proteins, and DNA. The plants response to metal toxicity involves several biological processes that require fine and precise regulation at transcriptional and post-transcriptional levels. MicroRNAs (miRNAs) are 21 nucleotide non-coding RNAs that regulate gene expression at the post-transcriptional level. A miRNA, incorporated into a RNA-induced silencing complex, promotes cleavage of its target mRNA that is recognized by an almost perfect base complementarity. In plants, miRNA regulation is involved in development and also in biotic and abiotic stress responses. We review novel advances in identifying miRNAs related to metal toxicity responses and their potential role according to their targets. Most of the targets for plant metal-responsive miRNAs are transcription factors. Information about metal-responsive miRNAs in different plants points to important regulatory roles of miR391, miR399, and miR398. The target of miR391 is the TCP transcription factor, implicated in growth control. miR399 exerts its action through the biogenesis of trans-acting small interference RNAs that, in turn, regulate auxin responsive factors. miR393 targets the auxin receptors TIR1/IAA and a bHLH transcription factor. Increasing evidence points...

Keywords: microRNAs, metal toxicity, abiotic stress
Small and/or large non-protein coding RNAs (npcRNAs) may be involved in the regulation/signaling of metal toxicity response (Jones-Rhoades et al., 2006; Hobert, 2008; Ben Amor et al., 2009). One of the most studied classes of npcRNAs is the micro RNAs (miRNAs). miRNAs are 21 nucleotide npcRNAs that regulate gene expression at the post-transcriptional level in plants. A precursor miRNA (pre-miRNA) with imperfect hairpin structure is processed into a mature miRNA and this is incorporated into a RNA-induced silencing complex (RISC) that promotes degradation/cleavage of the corresponding target mRNA(s), recognized by an almost perfect base complementarity with the miRNA (Jones-Rhoades et al., 2006). Though most of the miRNAs identified in Arabidopsis thaliana are related to plant development, there is evidence of the role of miRNAs in the plant response to different abiotic stresses including metal toxicity (Jones-Rhoades and Bartel, 2004; Fujii et al., 2005; Sunnkar et al., 2006; Phillips et al., 2007; Reyes and Chua, 2007; Li et al., 2008).

**MiRNAs and their Targets in Metal Toxicity**

Analyses of small RNAs expression profiles performed in plants exposed to metal toxicities has shown the differential expression of miRNA and their targets, thus indicating their possible role in regulation/signaling pathways. To determine the role of a specific miRNA it is important to analyze the function of its target(s) and their possible interactions with signaling pathways related to metal toxicity responses. Most of the targets predicted for metal-responsive conserved miRNAs are TF mainly involved in plant development (Table 1). Up-regulation of a certain miRNA resulting in its target degradation might indicate the target role as a negative regulator of metal toxicity response. Recent high-throughput genomic technologies as well as other genetic approaches have increased our current knowledge of miRNAs and their target in signaling pathways for metal toxicities response in several plant species (Sunkar and Zhu, 2004; Phillips et al., 2007; Huang et al., 2009; Ding et al., 2011; Chen et al., 2012; Zhou et al., 2012).

In regard to miRNAs that respond to Cd-toxicity the conserved miRNAs: miR160, miR164, and miR167 and the novel of Osa-miR602 and Osa-miR604 were identified in a library of small RNAs from rice seedlings exposed to Cd (Huang et al., 2009). Osa-miR602 is up-regulated in rice roots exposed for 12 h to high Cd; its predicted target is a xylem-solute to endoreduplication/endoreplication/lase-hydrolase. Osa-miR604, which was up-regulated in leaves treated with toxic levels of Cd for 6 h, down-regulated a lipid transfer protein (LPT; Huang et al., 2009). This type of protein is responsive to environmental stresses and to abscisic acid, salicylic acid, ethylene, and methyl jasmonate that has been proposed to participate in cutin and wax assembly and in defense of plant against pathogens (Arnedd et al., 2000; Kim et al., 2008). Rice microarray data showed that miR5328 is up-regulated, while miR162, miR166, miR171, miR390, miR168, and miR156 families were down-regulated under Cd stress (Ding et al., 2011). The search of possible metal-responsive cis-acting elements revealed that a MIRE-like sequence (5′-TCGGCGC-3′) is present in promoter regions of most of the Cd-responsive miRNA genes (Ding et al., 2011). Other cis-acting elements related to different abiotic stresses such as ARE (anaerobic-responsive element); ABRE (ABA-responsive element); GARE (gibberellins-responsive element); ERE (ethylene-responsive element); HSE (heat stress-responsive element); and LTR (low temperature-responsive element) were also identified in these miRNA genes promoters, thus implying that these miRNAs could be responsive to other stress signals besides metal toxicity (Ding et al., 2011). In roots of Brassica napus miR393, miR171, miR156, and miR396 are down-regulated after Cd exposure (6 h; Xie et al., 2007).

| Table 1 | Metal toxicity-responsive miRNAs. |
|----------------------------------|----------------------------------|
| Related metal        | miRNA | Targets                  | Reference                   |
| Cd, Hg, Al, Mn        | miR319| TCP transcription factors| Zhou et al., 2008; Valdés-López et al., 2010; Chen et al., 2012 |
| Cd, Hg, Al            | miR171| SCL transcription factors| Xie et al., 2007; Zhou et al., 2008, 2012 |
| Cd, Hg, Al            | miR368| TASS                     | Ding et al., 2011; Chen et al., 2012; Zhou et al. 2012 |
| Cd, Hg, Al            | miR393| TIR1/AFB (F-box auxin receptor) and bHLH transcription factors | Xie et al., 2007; Zhou et al. 2008 |
| Cd, Hg, Al            | miR396| GFP transcription factors | Xie et al., 2007; Chen et al., 2012; Zhou et al., 2012 |
| Cd, Hg, Mn            | miR167| Auxin responsive factors (ARFs)| Huang et al., 2009; Valdés-López et al., 2010; Zhou et al., 2012 |
| Cd, Hg                | miR164| NAC, CUP transcription factors | Huang et al., 2009; Zhou et al., 2012 |
| Cd, Al                | miR160| Auxin responsive factors (ARFs) | Huang et al., 2009; Chen et al., 2012 |
| Cd                    | miR156| SBP transcription factors | Xie et al., 2007; Ding et al., 2011 |
| Cu, Fe, Mn            | miR368| CSD, COP1b-1, CCS        | Sunkar et al., 2006; Zhou et al., 2008; Valdés-López et al., 2010 |
| Hg, Mn                | miR172| AP2 transcription factors | Valdés-López et al., 2010; Zhou et al., 2012 |
| Mn                    | miR397| Laccases                 | Valdés-López et al., 2010 |

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In leaves of the model legume *Medicago truncatula* miR393, miR171, miR319, and miR329 are up-regulated, while miR166 and miR398 are down-regulated after Cd, Hg, and Al exposure (24 h; Zhou et al., 2008). A high-throughput small RNA-sequencing approach revealed that miR159, miR160, miR319, miR396, and miR390 were down-regulated in response to Al (Chen et al., 2012). More recently a study using a similar approach identified Hg-toxicity responsive miRNAs such as the miR167, miR172, miR169, miR164, miR395 families that are up-regulated, whereas the miR396, miR390, and miR171 are down-regulated in this legume. In addition, new *M. truncatula* Hg-responsive miRNAs were identified such as miR2681 targets the transcripts coding TIR-NBS-LRR disease resistance proteins (Zhou et al., 2012).

Our group has reported the miRNA expression profile in common bean (*P. vulgaris*), the most important legume for human consumption. Using a miRNA-macroarray hybridization approach we identified miRNAs that respond to nutrient deficiencies and to Mn-toxicity in different plant organs. In common bean plants exposed to high Mn miR397 is down-regulated in leaves, miR319 and miR398 are up-regulated in roots and nodules, miR172 is up-regulated in nodules and miR167 is up-regulated in roots (Valdés-López et al., 2010). Recently, the identification and characterization of miRNAs in *P. vulgaris* by high-throughput sequencing has been completed (Peláez et al., 2012).

Current information about metal-responsive miRNAs in different plant species indicates the common relevant role of miR319, miR390, miR393, and miR398.

### ROLES OF miR319, miR390, miR393, AND miR398

#### miR319

Plant growth and senescence are processes affected by metal toxicity (Maksymiec, 2007). Common responses of shoots to Al- and Cu-toxicity include cellular and ultrastructural changes in leaves, decreased photosynthetic activity leading to chlorosis and necrosis of leaves, total decrease in leaf number and size, and decreased shoot biomass (Thornton et al., 1986; Lanaras et al., 1993; Maksymiec, 1997; Panou-Filotheou et al., 2001). In addition, Ca-tolerance leads to rapid senescence in leaves (Luna et al., 1994). Interestingly, miR319 and its target TCP (Teosinte Branched/Cycloidea/PCF) TF (Table 1), implicated in growth control, have shown differential expression in most of the studies of miRNAs responding to metal toxicity. Members of the TCP family bind to promoter elements which are essential for the expression of the proliferating cell nuclear antigen (PCNA) gene (Kosugi and Ohashi, 1997). Other TCPs are involved in the morphogenesis of shoot lateral organs (Li et al., 2005). Lately, it has been demonstrated that miR319 plays a role on leaf senescence through the regulation of TCPs that positively control leaf senescence via IA biosynthesis and important senescence positive regulators like WRKY33 (Schommer et al., 2008).

**Figure 1** depicts the mode of action of miR319 and TCP. In leaves, high Cd, Hg, and Al induce miR319 leading to the degradation of TCP thus affecting growth and senescence. In the roots, this miRNA is repressed in response to Al while it is induced in Mn-toxicity (Valdés-López et al., 2010; Chen et al., 2012). The opposite regulation of miR319 could be due to the different plant species and/or the different time of exposure and metal concentration used. When both metals are abundant in the ground Al may exert an antagonistic effect on the uptake of Mn thus ameliorating Mn-toxicity (Blair and Taylor, 1997; Yang et al., 2009). There are no reports about the regulation of miR319 when plant roots are exposed to the combination of Al and Mn; we find difficult to speculate about this issue since specific effects in the plant would depend on several variables (concentration, time of exposure, environmental conditions).

#### miR390

miR390 and its target TAS3 (Table 1) are related to metal toxicity response in different plants. The miR390-induced cleavage of TAS3 transcript initiates ta-siRNAs (trans-acting small interference RNAs) biogenesis, leading to the degradation of ARFs (auxin response factors) that play critical roles in lateral root development (Muirin et al., 2010). miR390 is repressed in roots of plants under Cd, Al, and Hg toxicities, which would lead the accumulation of intact TAS3 transcript and the decrease of tasiARFs resulting in...
and miR390 may play relevant regulatory roles. The root is the main organ affected by high concentration of metals such as Cu, Cd, Cu, Hg, and Al in the soil, and the common stress is manifested as changes in architecture (Karataglis et al., 2011).

Pseudomonas syringae delivers Cu to CSDs (Abdel-Ghany et al., 2005). Beauclair et al. (2010) proposed that the regulation of CCS1 by miR398 could be responsible for the unchanged protein levels of CSD1 and CSD2 in studies of plants expressing miR398-resistant forms of CSD1 or CSD2 (Dugas and Bartel, 2008). Furthermore, miR398 has a role in biotic stress. This miRNA decreases in Arabidopsis leaves infiltrated with avirulent strains of Pseudomonas syringae pv. tomato, CSD1 was negatively correlated with miR398 levels. Avirulent strains induce a biphasic accumulation of ROS (oxidative burst) leading to the accumulation of ROS at the beginning of the hypersensitive response and at a second phase accompanied by local cell death (Lamb and Dixon, 1997; Wojtaszek, 1997; Torres et al., 2006). Plants exposed to virulent strains do not show drastic changes in the levels of miR398, which could be due to the absence of the oxidative burst or to the presence of the initial accumulation of ROS (Lamb and Merchant, 1995; Quinlan et al., 2000). Oxidative stress suppresses miR398 expression that is essential for the accumulation of CSD1 and CSD2 transcripts (Figure 1). miR398 is down-regulated upon exposure to heavy metals such as Cu2+, Fe3+, high light, MV, ozone, salinity, and the biotic stress (avirulent strains) is the accumulation of ROS. The generation of ROS is one of the common responses to metal toxicities as well as the synthesis of active antioxidative enzymes. Both responses vary among different metal exposures (Sharma and Dietz, 2009), the specific response of miR398 or other ROS-responsive miRNAs may vary according to the metal and to the time of exposure to the stress (Figure 1).

CONCLUDING REMARKS

The identification and analysis of miRNAs responsive to different metal toxicities has provided information about their possible roles in the networks involved in plant adaptation to these abiotic stresses. These studies are recent so we can predict the discovery of additional novel metal stress-responsive miRNAs.
Further research is needed to deeply understand the role of miRNAs and their targets, mainly TFs, as main players in signaling pathways of plants to environmental changes. This should take into account that plant species varying in growth and genotypic backgrounds may have differential responses to metal toxicities exposure, including different metal concentration and combinations of metals, which will be helpful for obtaining better mechanistic insights into the roles of miRNAs in metal detoxification networks. To elucidate novel roles of miRNAs in the response to metal toxicities it is important to perform phenotypic analysis of plants with modulated expression of a specific miRNA and/or its respective targets.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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