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REVIEW
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Manganese in Plants: From Acquisition to Subcellular Allocation

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Manganese (Mn) is an important micronutrient for plant growth and development and sustains metabolic roles within different plant cell compartments. The metal is an essential cofactor for the oxygen-evolving complex (OEC) of the photosynthetic machinery, catalyzing the water-splitting reaction in photosystem II (PSII). Despite the importance of Mn for photosynthesis and other processes, the physiological relevance of Mn uptake and compartmentation in plants has been underrated. The subcellular Mn homeostasis to maintain compartmented Mn-dependent metabolic processes like glycosylation, ROS scavenging, and photosynthesis is mediated by a multitude of transport proteins from diverse gene families. However, Mn homeostasis may be disturbed under suboptimal or excessive Mn availability. Mn deficiency is a serious, widespread plant nutritional disorder in dry, well-aerated and calcareous soils, as well as in soils containing high amounts of organic matter, where bio-availability of Mn can decrease far below the level that is required for normal plant growth. By contrast, Mn toxicity occurs on poorly drained and acidic soils in which high amounts of Mn are rendered available. Consequently, plants have evolved mechanisms to tightly regulate Mn uptake, trafficking, and storage. This review provides a comprehensive overview, with a focus on recent advances, on the multiple functions of transporters involved in Mn homeostasis, as well as their regulatory mechanisms in the plant's response to different conditions of Mn availability.

Keywords: manganese transport, manganese uptake, manganese deficiency, manganese toxicity, intracellular distribution, Arabidopsis, rice, barley

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INTRODUCTION

Manganese (Mn) is an essential element in virtually all living organisms where it can fulfill two different functions: acting as an enzyme cofactor or as a metal with catalytic activity in biological clusters (Andresen et al., 2018). In humans, Mn functions as a cofactor for a variety of enzymes, including arginase, glutamine synthetase, pyruvate carboxylase, and Mn superoxide dismutase (MnSOD). But in comparison to other essential micronutrients, such as iron (Fe) and zinc (Zn), whose deficiencies in humans are responsible for major health problems, Mn deficiency in humans is rare. However, Mn poisoning may be encountered more frequently upon overexposure to this metal causing hepatic cirrhosis, polycythemia, dystonia, and Parkinson-like symptoms (Li and Yang, 2018). In plants, Mn is one of the 17 essential elements for growth and reproduction. It is needed in only small quantities by plants, but is ultimately as critical to growth as are the other nutrients. In photosynthetic organisms, Mn is an essential element of the metalloenzyme cluster

of the oxygen-evolving complex (OEC) in photosystem II (PSII). In spite of its importance for photosynthetic activity, Mn homeostasis in plants has been poorly investigated. Nevertheless, Mn deficiency can be a serious plant nutritional disorder in soils with high pH and high partial pressure of O_2 (pO_2), where the bio-availability of Mn can decrease far below the level that is required for normal plant growth (Broadley et al., 2012). Fertilization with Mn salts at soil level is often not effective, since soluble Mn (Mn^{2+}) is rapidly converted to plant-unavailable Mn oxides, particularly in sandy alkaline soils. (In this review, we use the general term "Mn," unless we refer to a specific oxidation state). However, it has been argued that the application of Mn fertilizers to the soil can be an effective way to alleviate Mn deficiencies, but only if soil pH is also corrected (White and Greenwood, 2013). Foliar Mn application can supply sufficient Mn to overcome Mn deficiency, but this strategy is expensive and often impractical for farmers on marginal lands. Moreover, foliar Mn sprays are only effective for a limited time period since Mn is very little mobile in the plant and does not remobilize from older leaves to Mn-deficient young leaves (Li et al., 2017). On the other extreme, Mn toxicity can occur in poorly drained and in strongly acidic soils, where it is usually associated with other acidity-related soil fertility problems, such as aluminum toxicity and deficiencies of calcium (Ca), magnesium (Mg), and molybdenum (Mo) (Goulding, 2016).

Depending on Mn availability, plants either need to efficiently acquire and utililize Mn under limiting conditions, or to detoxify the metal under superfluous supply. Transport processes are at the core of those adaptations. In the past, Mn transporters have been identified at the molecular level in many eukaryotic organisms (Pittman, 2005). Furthermore, recent progress in Mn homeostasis has mainly focused on Arabidopsis and rice, which represent dicot and graminaceous monocot plants, respectively (Socha and Guerinot, 2014; Shao et al., 2017). Only recently, transporters involved in uptake and subcellular distribution of Mn have been characterized in a wider range of plant species. This article reviews the current knowledge of Mn uptake, translocation and subcellular distribution, as well as the functions of Mn in different plant species. **Table 1** lists the Mn transporters discussed in the text.

FUNCTIONS OF MANGANESE IN PLANTS

Mn plays a role in diverse processes of a plant's life cycle such as photosynthesis, respiration, scavenging of reactive oxygen species (ROS), pathogen defense, and hormone signaling. In Arabidopsis, 398 enzymes are predicted to contain Mn in the metal-binding site (The UniProt Knowledgebase[1]). Among them, 20% showed an experimental evidence to require Mn as a cofactor. In many enzymes, Mn is interchangeable with other divalent cations such as Ca, cobalt (Co), copper (Cu), Mg, or Zn. In plants, only the OEC in PSII, MnSOD, and oxalate oxidase have been shown to require exclusively Mn.

The most-well-studied function in plant metabolism that depends on Mn is the water-splitting reaction in PSII, which is the first step of photosynthesis. This process requires the tetra-Mn cluster Mn_4O_5Ca to split two water molecules into four electrons, four protons, and molecular O_2 (Bricker et al., 2012). However, the delivery of Mn^{2+} and Ca^{2+} to the OEC reaction center in land plants is still under investigation. In the unicellular photosynthetic organism *Synechocystis*, PratA functions as an assembly factor and chaperone protein for efficient delivery of Mn to the PSII reaction core (Stengel et al., 2012). In green plants, it is speculated that the extrinsic protein PsbP, the closest homolog to PratA, acts as a Mn carrier protein to introduce Mn into the OEC reaction center, where it subsequently stabilizes the Mn cluster in association with PsbO and PsbQ (Bondarava et al., 2007).

Another process in plants dependent on Mn is the detoxification of ROS. In plant cells, ROS are formed mainly in chloroplasts, mitochondria, peroxisomes, and in the cytosol. Mn is a cofactor of MnSODs located in mitochondria as also in peroxisomes (Bowler et al., 1994; Corpas et al., 2017). In addition, oxalate oxidase is a Mn-dependent enzyme which catalyzes the oxidation of oxalate to CO_2 coupled with a reduction of O_2 to H_2O_2 (Requena and Bornemann, 1999). Oxalate oxidase is located in the apoplast, where it is involved in pathogen defense likely by the generation of microcidal concentrations of H_2O_2 and by the formation of effective barriers against pathogen penetration by H_2O_2-mediated lignification (Lane, 2002). Oxalate oxidase activity has been identified mainly in monocot plant species including wheat, barley, and rice (Svedruzic et al., 2005). Interestingly, germin-like proteins (GLPs) in Arabidopsis, which are homologous to oxalate oxidase, showed neither oxalate oxidase activity nor a Mn-dependent activation (Membré et al., 2000; Li et al., 2016). Intriguingly, the Mn^{2+} cation itself may act as an antioxidant molecule. In fact, it has been shown in yeast that elevated intracellular Mn was associated with a reduction of oxidative damage in yeast cells (Reddi et al., 2009). It is likely that Mn-phosphate (Mn-P) complexes act as antioxidants whereby the Mn speciation is altered by changes in phosphate concentrations (McNaughton et al., 2010).

Furthermore, Mn is an important cofactor of enzymes involved in isoprenoid biosynthesis (Wilkinson and Ohki, 1988; Köllner et al., 2008). Mn and Mg are two major cofactors of terpene synthases (Rohdich et al., 2006; Köllner et al., 2008). Therefore, it has been proposed that different patterns of plant terpene profiles are often closely correlated with Mg/Mn ratios rather than with concentrations of each cofactor element alone in the growth media (Farzadfar et al., 2017). Beside this, Mn is involved in lignin biosynthesis at two different levels: (i) Mn, besides Mg, can serve as cofactor of the phenylalanine ammonia-lyase (PAL) (Engelsma, 1972), a key enzyme in the phenylpropanoid pathway to produce monolignols; (ii) Lignin can be synthesized from monolignols that are oxidized by Mn^{3+} into monolignol radicals, which can then be added to existing phenolic groups to form lignin polymers (Önnerud et al., 2002).

[1] http://www.uniprot.org, accessed 20 October 2019

Intriguingly, it has been shown that Mn can replace Mg in the active site of some enzymes of the photosynthetic pathway, including Ribulose-1,5-bisphosphate carboxylase/oxygenase (Rubisco), changing the functional role of these enzymes (Bloom and Lancaster, 2018; Bloom, 2019). Furthermore, *in vitro* experiments demonstrated that Mn is an important cofactor in abscisic acid (ABA) and auxin signaling by activating PP2C phosphatases and IAA-amino acid conjugate hydrolases, respectively (LeClere et al., 2002; Meinhard et al., 2002; Schweighofer et al., 2004). Since diverse Golgi-localized glycosyl transferases require Mn for their activity, Mn is also essential for protein glycosylation and the biosynthesis of pectin and hemicellulose polymers (Egelund et al., 2006; Strasser et al., 2007; Basu et al., 2015). Other enzymes that require Mn as a cofactor are purple acid phosphatases (PAPs) (Schenk et al., 1999; Venkidasamy et al., 2019). Also, different decarboxylases (e.g., NAD malic enzyme) and dehydrogenases (e.g., phosphoenolpyruvate carboxylase) of the tricarboxylic acid cycle can be activated by Mn, but in many cases Mn can be replaced by Mg (Burnell, 1988; Gregory et al., 2009).

Another Mn-dependent process lies in the deposition of cuticular waxes in leaves. In barley, it has been demonstrated that Mn deficiency may decrease the cuticular wax layer, which leads to a higher transpiration rate (Hebbern et al., 2009). Moreover, Mn deficiency caused a decrease of cuticular waxes in Arabidopsis leaves (Alejandro et al., 2017).

In addition, Mn plays a role in such diverse processes as chloroplast development (Rohdich et al., 2000; Hsieh et al., 2008), purine and urea catabolism (Werner et al., 2008; Cao et al., 2010), phospholipid biosynthesis (Collin et al., 1999; Nowicki et al., 2005), Ca^{2+} signaling (Kim et al., 2003; Hashimoto et al., 2012), DNA repair (Takahashi et al., 2007; Szurmak et al., 2008), or histidine biosynthesis (Glynn et al., 2005).

MANGANESE DEFICIENCY AND TOXICITY

In plants, Mn deficiency often occurs as a latent disorder, without clear visual symptoms. Thus, the magnitude to which Mn deficiency affects crop yield is difficult to quantify. The critical concentration for Mn deficiency is generally below 10–20 $mg.kg^{-1}$ dry weight (Broadley et al., 2012). One of the consequences of Mn deficiency in plants is an impaired growth, leading to a decrease in biomass (Longnecker et al., 1991; Hebbern et al., 2005; Pedas et al., 2005). This can be caused by lower numbers of chloroplasts, lower net photosynthetic efficiency, and a decrease in chlorophyll content

TABLE 1 | Manganese transport proteins reviewed in this article.

Family/name	Organ(s)/tissue(s) expression	Subcellular localization	Gene expression response	Other substrates	References
CaCA					
AtCAX2	Root (stele and root tip), stem, leaf, flower, pollen, fruit	Tonoplast	Unaffected by +Cu, +Mn, +Zn	Ca, Cd	Hirschi et al., 2000; Shigaki et al., 2003; Pittman et al., 2004; Edmond et al., 2009
AtCAX4	Root, stem, leaf, flower, fruit	Tonoplast	Up-regulated by +Mn, +Ni, -Ca	Cd, Ca, Zn	Cheng et al., 2002; Koren'kov et al., 2007; Mei et al., 2009
AtCAX5	Root, stem, leaf, flower, fruit	Tonoplast	Up-regulated by +Mn down-regulated by +Zn	Ca	Edmond et al., 2009
HvCAX2	Root, leaf, seed	–	Up-regulated by +Ca, +Na unaffected by +Mn	Ca	Edmond et al., 2009
LeCAX2	Root, leaf, fruit	–	–	Ca	Edmond et al., 2009
OsCAX1a	Root, shoot, flower, seed	Tonoplast	–	Ca	Kamiya et al., 2005
OsCAX3	Root, shoot, flower, seed	–	–	Ca	Kamiya et al., 2005
OsCAX4	Root	–	Up-regulated by +Ca	Ca,Cu	Yamada et al., 2014
VvCAX3	Root, stem, leaf, fruit	Tonoplast	Up-regulated by +Ca, +Na unaffected by +Mn	Ca, Cu, Li, Na	Martins et al., 2017
AtCCX3	Root, stem, leaf, flower	Tonoplast, endomembranes	Up-regulated by +K, +Na unaffected by +Mn	K, Na	Morris et al., 2008
BICAT					
AtBICAT1/PAM71/CCHA1	Leaf	Chloroplast (thylakoid membrane)	Unaffected by +Mn	Ca	Schneider et al., 2016; Wang et al., 2016; Eisenhut et al., 2018; Frank et al., 2019
AtBICAT2/CMT1	Root, stem, leaf, flower, fruit	Chloroplast (inner envelope)	Down-regulated by +Mn	Ca, Mg	Eisenhut et al., 2018; Frank et al., 2019; Zhang et al., 2018

(Continued)

TABLE 1 | Continued

Family/name	Organ(s)/tissue(s) expression	Subcellular localization	Gene expression response	Other substrates	References
CDF/MTP					
AtMTP8	Root (epidermis, cortex), seed	Tonoplast	Up-regulated by +Mn -Fe	Fe	Eroglu et al., 2016, 2017
AtMTP9	–	–	Unaffected by +Mn	–	Delhaize et al., 2007; Chu et al., 2017
AtMTP10	–	–	Unaffected by +Mn	–	Delhaize et al., 2007; Chu et al., 2017
AtMTP11	Root (root tip), leaf (guard cells)	Golgi/PVC	Unaffected by +Mn	–	Delhaize et al., 2007; Peiter et al., 2007
ShMTP8	–	Tonoplast	–	–	Delhaize et al., 2003, 2007
BmMTP10	Root, leaf	Endomembranes*	Up-regulated by +Mn	–	Erbasol et al., 2013
BmMTP11	Root, leaf	Endomembranes*	Unaffected by +Mn	Ni	Erbasol et al., 2013
OsMTP8.1	Root, shoot	Tonoplast	–	–	Chen et al., 2013; Takemoto et al., 2017
OsMTP8.2	Root, shoot	Tonoplast	–	–	Takemoto et al., 2017
OsMTP9	Root (endodermis, exodermis)	Plasma membrane	Unaffected by +Mn -Mn		Ueno et al., 2015
OsMTP11	Root, shoot	Golgi/TGN	Up-regulated by +Mn +Zn +Cd +Ni	Co, Ni	Zhang and Liu, 2017; Ma et al., 2018; Tsunemitsu et al., 2018
HvMTP8.1	Root, leaf	Golgi	Down-regulated by -Mn (root) down-regulated by +Mn (shoot)	–	Pedas et al., 2014
HvMTP8.2	Root, leaf	Golgi	Down-regulated by +Mn	–	Pedas et al., 2014
PtMTP11.1	–	TGN	–	–	Peiter et al., 2007
PtMTP11.2	–	TGN	–	–	Peiter et al., 2007
PbMTP8.1	–	–	–	Fe	Hou et al., 2019
PbMTP8.2	–	–	–	Fe	Hou et al., 2019
PbMTP9	–	–	–	Fe	Hou et al., 2019
PbMTP10	–	–	–	Fe	Hou et al., 2019
PbMTP11.1	–	–	–	–	Hou et al., 2019
PbMTP11.2	–	–	–	–	Hou et al., 2019
NtMTP8.1	Root, stem, leaf, flower	–	Up-regulated by +Co +Zn unaffected by +Mn	–	Liu et al., 2019
NtMTP8.4	Stem, leaf, flower	–	Up-regulated by +Cd +Co +Mn (root) up-regulated by +Cd +Co +Mg +Zn (shoot)	–	Liu et al., 2019
NtMTP11.1	Root, stem, leaf, flower	–	Up-regulated by +Co +Cd +Mn +Zn	–	Liu et al., 2019
CsMTP9	Root (endodermis)	Plasma membrane	Up-regulated by +Cd +Mn +Ni down-regulated by –Mn -Zn	Cd	Migocka et al., 2015
NRAMP					
AtNRAMP1	Root (Cortex, endodermis) > > shoot	Plasma membrane	Up-regulated by -Fe -Mn	Cd, Fe	Curie et al., 2000; Thomine et al., 2000; Cailliatte et al., 2010; Castaings et al., 2016
AtNRAMP2	Root (pericycle, root tip), leaf vasculature, flower, trichome	TGN	Up-regulated by -Mn down-regulated by -Fe	–	Curie et al., 2000; Alejandro et al., 2017; Gao et al., 2018

(Continued)

TABLE 1 | Continued

Family/name	Organ(s)/tissue(s) expression	Subcellular localization	Gene expression response	Other substrates	References
AtNRAMP3	Root (stele), leaf vasculature, developing seed	Tonoplast	Up-regulated by -Fe unaffected by -Mn	Cd, Fe	Thomine et al., 2000, 2003; Lanquar et al., 2005, 2010
AtNRAMP4	Root (stele), leaf vasculature, developing seed	Tonoplast	Up-regulated by -Fe unaffected by -Mn	Cd, Fe	Thomine et al., 2000; Lanquar et al., 2005, 2010
OsNRAMP3	Node, leaf vasculature	Plasma membrane	Unaffected by +Mn -Mn	–	Yamaji et al., 2013; Yang et al., 2013
OsNRAMP5	Root (exodermis, endodermis, stele), panicle	Plasma membrane	Up-regulated by -Fe (shoot) up-regulated by -Fe, -Zn (root) unaffected by -Mn	Cd, Fe	Ishimaru et al., 2012; Sasaki et al., 2012; Yang et al., 2014
OsNRAMP6	Leaves	Plasma membrane	–	Fe	Peris-Peris et al., 2017
HvNRAMP5	Root (epidermis, stele)	Plasma membrane	Up-regulated by -Fe unaffected by +Mn	Cd	Wu et al., 2016
BnNRAMP1b	Root, shoot	–	Up-regulated by +Cd	Cd, Zn	Meng et al., 2017
TcNRAMP3	–	Tonoplast	–	Cd, Fe	Oomen et al., 2009
TcNRAMP4	–	Tonoplast	–	Cd, Fe, Zn	Oomen et al., 2009
TcNRAMP3 (*T. cacao*)	Root, shoot	–	Up-regulated by -Fe unaffected by -Mn	Fe	Ullah et al., 2018
TcNRAMP5 (*T. cacao)*	Root	–	Up-regulated by -Fe unaffected by -Mn	Cd, Fe, Zn	Ullah et al., 2018
TcNRAMP6 (*T. cacao)*	Root, shoot	–	–	–	Ullah et al., 2018
LeNRAMP1	Root	Endomembranes*	up-regulated by -Fe	–	Bereczky et al., 2003
LeNRAMP3	Root, shoot	Endomembranes*	Up-regulated by -Fe	–	Bereczky et al., 2003
AhNRAMP1	Root, stem	–	Up-regulated by -Mn, -Zn	Zn	Wang et al., 2019
MbNRAMP1	Root	Endomembranes*	Up-regulated by -Fe	Fe	Xiao et al., 2008
P-TYPE ATPASE					
AtECA1	Root, stem, leaf, guard cells, trichome	ER	–	Ca, Zn	Liang et al., 1997; Wu et al., 2002; Li et al., 2008
AtECA3	Root (stele), stem, leaf vasculature, guard cells, flower, fruit	Golgi	Unaffected by -Mn	Ca, Zn	Mills et al., 2007; Li et al., 2008
LeLCA1	–	ER?	–	Ca	Johnson et al., 2009
VIT					
AtVIT1	Root, cotyledon, developing seed	Tonoplast	–	Fe	Kim et al., 2006
OsVIT1	Leaf > > root, stem, panicle, embryo	Tonoplast	Down-regulated by -Fe	Fe, Zn	Zhang et al., 2012; Wang et al., 2017
OsVIT2	Leaf, stem, panicle, embryo	Tonoplast	Up-regulated by +Fe down-regulated by -Fe	Fe, Zn	Zhang et al., 2012
TaVIT2	Root, shoot, seed	Tonoplast	–	Fe	Connorton et al., 2017
AtMEB1	–	ER bodies	–	Fe	Yamada et al., 2013
AtMEB2	–	ER bodies	–	Fe	Yamada et al., 2013
YSL					
OsYSL2	Root (phloem), leaf, vascular bundle, developing seed	Plasma membrane	Up-regulated by -Fe down-regulated by -Mn	Fe	Koike et al., 2004; Yang et al., 2014
OsYSL6	Root, shoot	Plasma membrane	Unaffected by +Mn -Mn	–	Sasaki et al., 2011
HvYSL2	Root (endodermis), shoot	–	Up-regulated by -Fe	Fe, Zn, Co, Ni, Cu	Araki et al., 2011

(Continued)

TABLE 1 | Continued

Family/name	Organ(s)/tissue(s) expression	Subcellular localization	Gene expression response	Other substrates	References
ZIP					
AtIRT1	Root (epidermis, cortex) > > shoot	Plasma membrane	Up-regulated by -Fe	Fe, Zn, Co, Ni	Korshunova et al., 1999; Curie et al., 2000; Thomine et al., 2000; Vert et al., 2002
AtZIP1	Root (stele), leaf vasculature	Tonoplast	Up-regulated by -Fe -Zn (root) up-regulated by -Mn (shoot) down-regulated by -Zn (shoot)	Zn	Milner et al., 2013
AtZIP2	Root (stele)	Plasma membrane	Down-regulated by -Fe -Mn	Zn	Milner et al., 2013
AtZIP5	Root, shoot	–	–	–	Milner et al., 2013
AtZIP6	Root, shoot	–	–	–	Milner et al., 2013
AtZIP7	Shoot > > root	–	–	Fe, Zn	Milner et al., 2013; Fu et al., 2017
AtZIP9	Root, shoot	–	–	–	Milner et al., 2013
HvIRT1	Root (epidermis, cortex**, endodermis**, pericycle), seed	Plasma membrane	Up-regulated by -Fe, -Mn	Fe, Zn	Pedas et al., 2008; Long et al., 2018
LeIRT1	Root, flower	–	–	Cd, Fe, Zn	Eckhardt et al., 2001
LeIRT2	Root	–	–	Cd, Fe, Zn	Eckhardt et al., 2001
MtZIP4	Root***, leaf	–	Down-regulated by -Fe -Mn up-regulated by +Zn	–	López-Millán et al., 2004
MtZIP7	Leaf	–	Unaffected by -Mn	–	López-Millán et al., 2004
PtIRT1	Root, leaf	–	Down-regulated by -Mn	Fe, Zn	Fu et al., 2017

*+ excess, − deficiency, * in yeast cells, ** only under +Fe, *** only under +Zn.*

(Henriques, 2004; Hebbern et al., 2009; Alejandro et al., 2017), as well as higher susceptibility to pathogen infections (Heckman et al., 2003; Heine et al., 2011), imbalance in plant water relations (Ohki, 1985; Hebbern et al., 2009), and decreased tolerance to low temperatures (Ihnatowicz et al., 2014; Stoltz and Wallenhammar, 2014). Mn deficiency leads to a reduced number of Mn-complexes in the PSII core, which causes the destabilization and disintegration of PSII complexes that lowers the net photosynthesis rate (Schmidt et al., 2016). Besides, the disintegration of PSII complexes directly affects the thylakoid structure and promotes chlorophyll degradation leading to the development of characteristic interveinal leaf chlorosis (Papadakis et al., 2007). Due to the low phloem mobility of Mn (Ferrandon and Chamel, 1988; Li et al., 2017), typical symptoms of Mn deficiency first develop in younger leaves. Pale mottled leaves and interveinal chlorosis are the most visible symptoms of the disorder (Schmidt et al., 2016). Under severe Mn deficiency, leaves may also develop gray speck symptoms, which are characterized by brownish or necrotic spots (Broadley et al., 2012). It has been proposed that necrotic spots are a consequence of an increase in free oxygen radicals in damaged chloroplasts and a decrease in MnSOD activity (Broadley et al., 2012; Hajiboland, 2012). Similar responses have been described in Chlamydomonas, where a decrease in photosynthesis and mitochondrial MnSOD function was observed under Mn-deficient conditions (Allen et al., 2007). However, Mn-starved Arabidopsis seedlings showed a decrease in net photosynthesis while there was no loss of MnSOD activity (Lanquar et al., 2010). This suggests that the use of the cellular Mn pool for Mn-requiring metabolic reactions under low Mn conditions is variable among photosynthetic organisms.

In roots, an increase in the frequency of root hairs can be observed under Mn deficiency (Yang et al., 2008). If the deficiency becomes more severe, root tips may develop serious necrosis (Yamaji et al., 2013).

Toxic Mn concentrations are highly dependent on plant species and genotypes (Husted et al., 2009; Broadley et al., 2012; Fernando and Lynch, 2015). Excess Mn may be stored in vacuoles (Dučić and Polle, 2007; Dou et al., 2009), cell walls (Führs et al., 2010), and distributed to different leaf tissues (Fernando et al., 2006a,b). Also, Mn can be chelated in Mn-P complexes in trichomes (McNear and Küpper, 2014; Blamey et al., 2015) and complexed by organic acids in leaves (Lambers et al., 2015). Therefore, it is likely that differences between plant species lie in the cellular distribution and speciation of Mn, dominated by complexes with malate or citrate (Fernando et al., 2010). At the molecular level, excessive Mn can prevent the uptake and translocation of other essential elements such as Ca, Mg, Fe, and P (Alam et al., 2005; St.Clair and Lynch, 2005; Blamey et al., 2015; Lešková et al., 2017), inhibit chlorophyll biosynthesis (Clairmont et al., 1986; Subrahmanyam and Rathore, 2001), cause a decline in the photosynthetic rate (Nable et al., 1988; Amao and Ohashi, 2008), reduce the meristematic cell division in roots by inhibiting auxin biosynthesis (Morgan et al., 1966;

Zhao et al., 2017), and lead to an increase in the accumulation of oxidized Mn and oxidized phenolic compounds in the apoplast (Fecht-Christoffers et al., 2006).

The symptoms of Mn toxicity vary widely among plant species, with chlorotic leaves and necrotic spots as the most common symptoms (Millaleo et al., 2010). Accordingly, Mn stress in plants has been explained by two main hypotheses based on either symplastic or apoplastic processes (Fernando and Lynch, 2015). The symplastic hypothesis proposes that Mn toxicity acts via photo-oxidative stress in the chloroplast that causes chlorosis. Conversely, in the apoplastic hypothesis, Mn stress damage is mainly due to the accumulation of Mn oxides, oxidized phenolic compounds, and ROS, in the cell wall, leading to necrosis. Necrotic spots have thus been associated with the accumulation and oxidation of Mn and of oxidized phenolic compounds, while chlorosis has been often attributed to Fe deficiency induced by high Mn. Surprisingly, necrotic spots are high in Mn and appear first on older leaves, whereas in chlorotic areas no Mn accumulation can be observed. It is hence conceivable that the mechanism resulting in necrotic spots differs from that which causes chlorosis.

Several lines of evidence suggest that the early target of Mn toxicity is the photosynthetic process (Millaleo et al., 2010). In fact, plants exposed to Mn excess showed a decline in net photosynthesis rate and chlorophyll content (Li et al., 2010). Although in chloroplasts the occurrence of thylakoid swelling has been associated with the administration of excess Mn (Lidon et al., 2004; Doncheva et al., 2009), the target of Mn in these photosynthetic membranes is still unclear. It has been proposed that the oxidation of Mn in chloroplasts by light-activated chlorophyll generates ROS, and thereby damages chlorophyll (Panda et al., 1987; Baldisserotto et al., 2007). At the same time, Mn may substitute Mg in chlorophyll molecules or bind to ferredoxin in the thylakoid matrix, eventually destroying the ultrastructure of chloroplasts (Panda et al., 1987; Hauck et al., 2003). Moreover, the lack of physiologically active Fe would be a secondary effect of Mn toxicity (Nian, 1989; Huang et al., 2016), which might block chlorophyll synthesis and the correct assembly of photosystem I (PSI) (Chereskin and Castelfranco, 1982; Cornah et al., 2002; Millaleo et al., 2013). Consequently, photoinhibition of PSII would likely be a late side effect of Mn exposure.

MANGANESE DYNAMICS IN SOIL

Mn is one of the most abundant and widely distributed metals in nature and comprises about 0.1% of the Earth's crust (Emsley, 2003). The element is found in minerals, combined with other elements such as oxygen, sulfur, carbon, silicon, and chlorine (Turekian and Wedepohl, 1961). Mn can exist in 11 oxidation states, ranging from −3 to +7, but in soils, Mn is mainly present as +2 (e.g., Mn^{2+}), +3 (e.g., Mn_2O_3) and +4 (e.g., MnO_2). Availability of Mn to plants depends on its oxidation state: Mn^{2+} is the only plant-available form and can be readily transported into root cells and translocated to the shoot, whereas the oxidized species Mn(III) and Mn(IV) form insoluble oxides that rapidly sediment (Stumm and Morgan, 1996). Thus, Mn dynamics in soils are mostly represented by the concept of a balance between soluble Mn^{2+} and insoluble Mn oxides (MnO_x).

Mn deficiency in plants is particularly prevalent in alkaline soils, in which the oxidization of Mn^{2+} to unavailable MnO_x is favored. Such soils are common in the northern part of Europe, the UK, USA, China, and in southern Australia (Husted et al., 2009; George et al., 2014). In addition to pH, the oxygen level (pO_2) in soil and soil microorganisms are also relevant factors of Mn dynamics in soils. Beside this, root exudates can modify the Mn availability in the rhizosphere. The Mn redox status in soils involves primarily the competition of soluble highly mobile oxidants, such as molecular O_2, and soluble reducing organic molecules, derived from soil organic matter and biological sources. In aerobic soils, due to the high mobility and redox potential of O_2, Mn oxidation is favored rather than reduction of MnO_x by microorganisms (Lovely, 1995). By contrast, waterlogging causes a reduction of MnO_x most likely by decreasing the O_2 concentration, leading to an increase of plant-available Mn^{2+} in soil solution up to toxic levels (Khabaz-Saberi et al., 2006).

However, it has been proposed that the oxidation of Mn^{2+} in environments with abundant O_2 is sluggish, particularly in the absence of biological catalysts, and that the oxidation of Mn^{2+} in soil is carried out predominantly by microorganisms (Sparrow and Uren, 2014). Indeed, microorganisms can catalyze Mn^{2+} oxidation in order of 10^3 times faster than abiotic oxidation (Morgan, 2005). Some microorganisms produce enzymes which directly oxidize Mn^{2+}, or produce extracellular superoxide leading to the production of insoluble MnO_x (Hansel et al., 2012; Zhang et al., 2014). Conversely, other microorganisms can reduce MnO_x and thereby increase Mn availability for plant uptake (Rengel, 2015). Also, environmental conditions (temperature, humidity) affect soil Mn availability by modulating the activity of Mn-oxidizing microorganisms (Sparrow and Uren, 2014). Therefore, the population of Mn-oxidizing and Mn-reducing microorganisms is a key factor in the availability of soil Mn for plant uptake.

Another important factor of Mn dynamics in soils is the exudation of protons (H^+), carboxylates, and enzymes by plant roots. Proton exudation increases the Mn availability in the rhizosphere by exchanging Mn that is immobilized by negatively charged organic matter and clay minerals, and also by lowering the pH of alkaline soils (Rengel, 2015). Mn uptake by some Mn-hyperaccumulators, such as *Phytolacca* species, is based on a strong rhizosphere acidification (Lambers et al., 2015). Noteworthy, Mn availability is also increased by root exudation of carboxylates which chelate Mn and reduce Mn(IV) to Mn^{2+} in either acidic or alkaline soils (Jauregui and Reisenauer, 1982; Gherardi and Rengel, 2004).

Phytate (inositol hexaphosphate) is generally the dominant form of organic P in soils and has the potential to complex Mn^{2+} and other divalent cations. Exudation of phytases, which catalyze the degradation of phytate thus increases the Mn availability by releasing Mn^{2+} (George et al., 2014).

The release of carboxylates into the rhizosphere is a mechanism for the acquisition of not only Mn, but in particular

of P. Carboxylates mobilize P absorbed to Fe/Al hydroxides by ligand exchange, especially under low P availability (Nuruzzaman et al., 2006). By contrast, elevated levels of soil-P lead to a reduction of carboxylate and phytase exudation, in turn decreasing Mn^{2+} acquisition (Lambers et al., 2015; Giles et al., 2017). However, hydroponic experiments in barley, where most likely no Mn–P complexes were formed, have also shown a decrease in Mn uptake under elevated P supply (Pedas et al., 2011). Hence, it has been proposed that there is a competition between Mn^{2+} and P during Mn uptake.

MANGANESE TRANSPORT PROTEINS IN PLANTS

As mentioned above, reduced Mn (Mn^{2+}) is the only available form for plants. To maintain an optimal supply, acquisition from the rhizosphere and distribution of Mn have to be regulated. One of the most important mechanisms to regulate the acquisition from the soil is the uptake by specific transporters into root cells (**Figure 1**). Once Mn reaches the symplast, the main pathways for the translocation and distribution of Mn in the whole plant involve transport toward and into the xylem, transfer to the phloem, and translocation to and between the different tissues. However, most of the Mn transporters and mechanisms required for Mn loading into the xylem of the root stele, for loading Mn into the phloem, and for Mn transport into the plant cell in shoots have not been identified yet. Interestingly, the mobility of Mn in the phloem is supposed to be low (Li et al., 2017), but there is evidence that a small amount of Mn may be recycled via the phloem. In fact, it has been reported that after application of ^{52}Mn to a cut barley leaf, radioactivity was detectable in the discrimination center of the shoot, in other leaves, as also in root tips (Tsukamoto et al., 2006). These results suggested that ^{52}Mn was transported by unknown transporters with low affinity.

An intriguing property of Mn transport across membranes is that most of the proteins that transport Mn are not specific for the metal. Plant Mn^{2+} transporters can transport, to varying extent, other divalent cations, such as Fe^{2+}, Zn^{2+}, Cu^{2+}, Cd^{2+}, Ca^{2+}, Co^{2+}, and Ni^{2+}. The physiological relevance of this low specificity needs further investigations, including the modification of specificity. For instance, in the Mn/Fe transporter AtMTP8, Fe transport activity was inhibited by introducing point mutations in different Fe-binding domains without affecting its Mn^{2+} transport capability (Chu et al., 2017).

Diverse families of transport proteins are known to be components of the Mn homeostatic network in plants and can be classified into importers and exporters. Importers translocate Mn from the extracellular space or from internal compartments into the cytosol, whereas exporters are responsible for the exclusion of Mn out of the cytosol into intracellular compartments or into the apoplast. The Natural Resistance Associated Macrophage Protein (NRAMP) family, the Zinc-Regulated Transporter/Iron-Regulated Transporter (ZRT/IRT)-related Protein (ZIP) family, and the Yellow Stripe-Like (YSL) family have members involved in the transport of Mn^{2+} into the cytosol. In contrast, the Cation Diffusion Facilitator/Metal Transport Protein (CDF/MTP) family, the Vacuolar Iron Transporter (VIT) family, the Ca^{2+}/Cation Antiporter (CaCA) superfamily, the Bivalent Cation Transporter (BICAT) family, and the P_{2A}-type ATPase family have members involved in the transport of Mn^{2+} out of the cytosol. **Figure 1** shows the tissue specificity and subcellular localization of Mn transport proteins in roots of Arabidopsis, rice, and other plant species. Genes encoding encoding Mn transport proteins in aerial parts of the plant species are depicted in **Figure 2**, and the subcellular localization of these proteins is displayed in **Figure 3**. The NRAMP family has been characterized in a number of species including bacteria, fungi, plants, and animals. These proteins act as metal/H^+ symporters and are capable of transporting divalent metal cations (Fe^{2+}, Mn^{2+}, Zn^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}) into the cytosol (Nevo and Nelson, 2006), with the exceptions of OsNRAMP4 (syn. OsNrat1), that transports the trivalent cation Al^{3+} (Xia et al., 2010; Li et al., 2014), and OsNRAMP1, that appears to mediate also As(III) transport (Tiwari et al., 2014).

The ZIP transporters have been found widely in bacteria, fungi, plants, and animals and are predicted to be involved in Fe^{2+}, Zn^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, and Mn^{2+} transport. They have 8 transmembrane domains (TMD) with extracellular N- and C-termini and a cytosolic histidine-rich loop (Guerinot, 2000). YSL transporters are related to the OligoPeptide Transporter (OPT) family and are exclusively found in plants, bacteria, fungi, and archaea. Members of the YSL family are predicted to transport metals (Mn^{2+}, Zn^{2+}, Cu^{2+}, Ni^{2+}, Cd^{2+}, Fe^{2+}) complexed to non-proteinogenic amino acids, such as nicotianamine (NA) or phytosiderophores (PS) (Schaaf et al., 2004).

The CDF family has members in all organisms. Most CDFs are Metal^{2+}/H^+(K^+) antiporters and mediate the efflux of Zn^{2+}, Co^{2+}, Fe^{2+}, Cd^{2+}, Ni^{2+}, and/or Mn^{2+}. Most of them have six TMDs with histidine-rich regions at their cytosolic N- and/or C-terminus and additionally between the 4th and 5th TMD. Based on phylogenetic relationships, the CDF family can be classified, corresponding to the main transported metal, into three major subgroups: Zn-CDFs, Fe/Zn-CDFs, and Mn-CDFs (Montanini et al., 2007).

BICAT proteins, also denominated Photosynthesis-Affected Mutant71 (PAM71) or Chloroplast Manganese Transporter (CMT) proteins, belong to the Uncharacterized Protein Family 0016 (UPF0016), which represents a new family of cation transporters present in all eukaryotes and prokaryotes, except in *Lactobacillales* and *Bacillales* (Demaegd et al., 2013, 2014; Hoecker et al., 2017). The protein structure of the plant homologs is characterized by two clusters of three transmembrane domains separated by a central loop. BICAT proteins act as Mn^{2+} and Ca^{2+} transporters (Hoecker et al., 2017; Frank et al., 2019).

CaCA transporters are present in all kingdoms of life and have a conserved core structure of ten transmembrane domains and two conserved α-repeat regions containing acidic amino acids (Pittman and Hirschi, 2016). In particular, the Cation/Ca^{2+} exchanger (CCX) and the H^+/Cation exchanger (CAX) families, which are both members of the CaCA superfamily, are present within all plants.

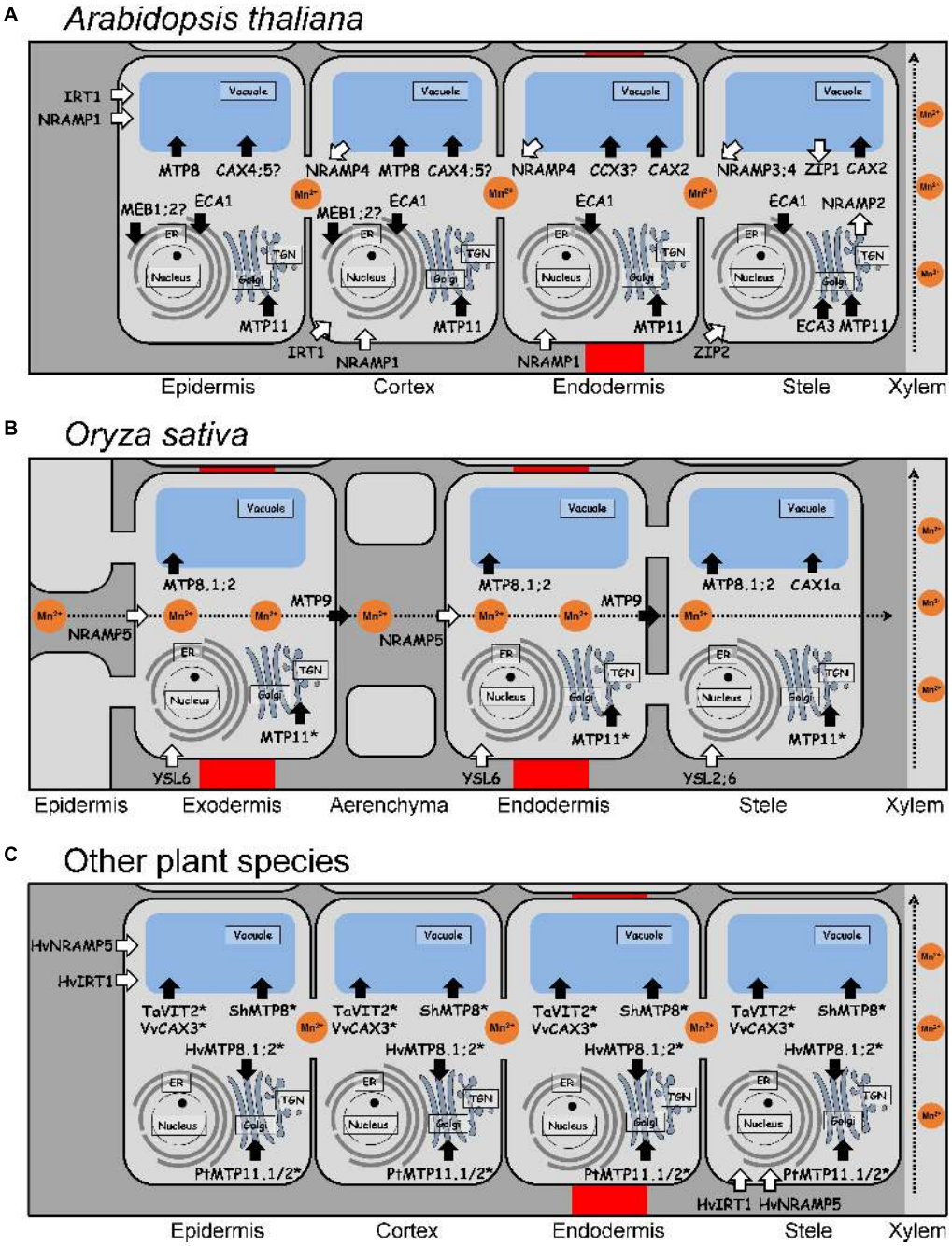

FIGURE 1 | Tissue specificity and subcellular localization of Mn transport proteins in roots of different plant species. **(A)** Mn transport proteins in epidermis, endodermis, cortex, and stele (including pericycle) of Arabidopsis roots. **(B)** Mn transport proteins in exodermis, endodermis, and stele of rice roots. Radial transport of Mn^{2+} is carried out by OsNRAMP5 and OsMTP9, which are polarly localized transporters at both the exodermis and the endodermis, providing a unidirectional flux of Mn from the soil to the stele (indicated as dashed arrow). **(C)** Mn transport proteins in epidermis, endodermis, cortex, and stele of roots of other plant species. **(A–C)** White arrows indicate import into the cytosol, black arrows indicate export out of the cytosol. Transport proteins with yet unknown root tissue specificity are marked by asterisks. Proteins which subcellular localization only shown in yeast but not in plants are indicated by a question mark. Hv, *Hordeum vulgare*; Pt, *Populus trichocarpa*; Sh, *Stylosanthes hamata*; Ta, *Triticum aestivum*; Vv, *Vitis vinifera*.

VIT transporters are found in plants, fungi, and bacteria, but are absent in animals. Members of the VIT family in plants share a high degree of sequence similarity and most of them are capable to transport Fe^{2+} in addition to Mn^{2+}, but their biological functions have been poorly investigated (Cao, 2019).

Plant P-type Ca^{2+}-ATPases are divided into two groups, 2A and 2B, whereby the first one does not contain an N-terminal

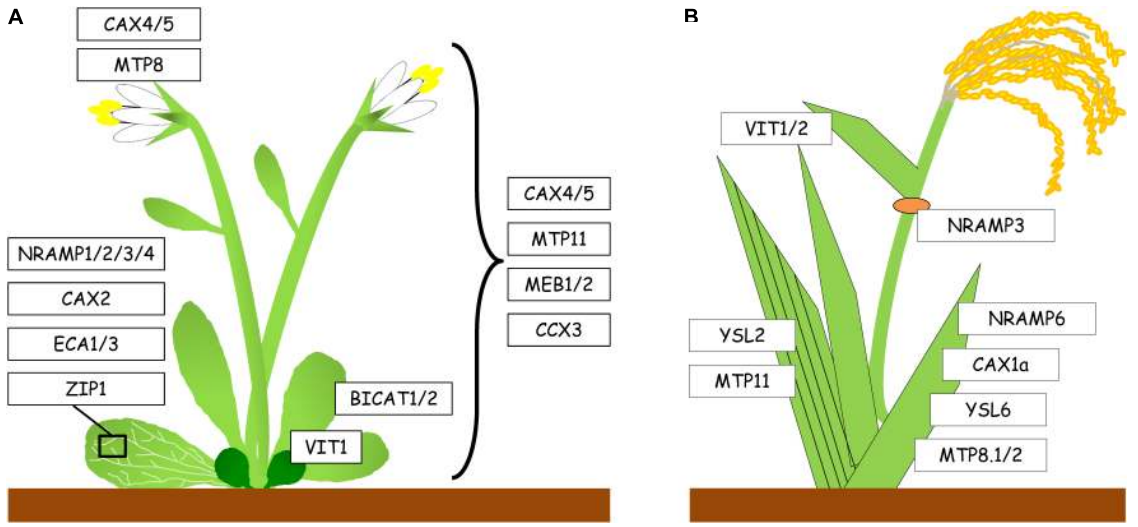

FIGURE 2 | Expression of genes encoding Mn transport proteins in aerial parts of Arabidopsis and rice. **(A)** Mn transport proteins in shoots of Arabidopsis. Transporters listed on the left are expressed in the vasculature of leaves, transporters listed on the right are expressed throughout the above-ground tissues of the plant. In vegetative tissues, *AtVIT1* is only expressed in cotyledons. **(B)** Mn transport proteins in shoots of rice. *OsMTP11* and *OsYSL2* are expressed in the vasculature. *OsNRAMP3* is expressed in the first node (orange). *OsYSL6* and *OsMTP8.1/2* are expressed in older leaves, whereas expression of *OsVIT1/2* is more pronounced in younger leaves.

autoinhibitory domain (Johnson et al., 2009). Those P_{2A}-type Ca^{2+}-ATPases have also a role in Mn^{2+} transport.

MANGANESE UPTAKE FROM THE SOIL AND TRANSLOCATION TO THE SHOOT

Despite the importance of Mn in plant physiology, our knowledge of systems mediating Mn uptake followed by translocation from the roots to the shoot is limited. This is mainly due to the lack of information about the expression and subcellular localization of Mn transporters in most plants. In fact, only few Mn transporters involved in uptake and root radial transport have been identified so far. Uptake of Mn^{2+} has been assumed to be mediated by plasma membrane Ca^{2+} channels, which are generally permeable to Mn^{2+} (Wymer et al., 1997; White et al., 2002). However, this is likely to be a minor Mn^{2+} uptake pathway due to its competition with Ca^{2+}, only relevant when Mn^{2+} is present in high concentrations. However, in soil, Mn^{2+} is usually far less abundant than Ca^{2+} (Broadley et al., 2012). Since this assumption, few Mn transporters have been identified mainly in *A. thaliana* and rice. Their tissue-specific localizations in roots are shown in **Figure 1A** for Arabidopsis, in **Figure 1B** for rice, and in **Figure 1C** for other plant species including barley, wheat, tomato, poplar, and grapevine.

In Arabidopsis, there is plenty of evidence that Mn^{2+} uptake is mainly mediated by AtNRAMP1 (**Figure 1A**), which is localized in the plasma membrane of epidermis and cortex cells in roots, and less in vascular tissues of young leaves (Cailliatte et al., 2010; Castaings et al., 2016). Under Mn-deficient conditions, the expression of *AtNRAMP1* is moderately up-regulated, and *nramp1* knockout mutants accumulate less Mn in shoots under Mn deficiency, which points to a function of this protein as a high-affinity Mn^{2+} uptake transporter (Cailliatte et al., 2010). *NRAMP1* orthologs in cacao, rapeseed, and peanut are also expressed in roots and complement a Mn uptake-deficient yeast strain, *smf1*, lacking a Mn transporter located in the plasma membrane (Meng et al., 2017; Ullah et al., 2018; Wang et al., 2019). In addition, active Mn^{2+} uptake may be accomplished by the ZIP transporter AtIRT1 (Castaings et al., 2016), that is considered as the major Fe uptake transporter of dicots. However, AtIRT1 is not strongly selective for Fe^{2+}, but also transports Zn^{2+}, Cu^{2+}, Co^{2+}, Ni^{2+}, and Mn^{2+} (Korshunova et al., 1999). *IRT1* orthologs expressed in roots have also been identified in tomato and trifoliate orange, but their function in Mn^{2+} uptake remains to be confirmed (Eckhardt et al., 2001; Fu et al., 2017). Furthermore, two ZIP transporters expressed in the root stele are described to be involved in root-to-shoot translocation of Mn in Arabidopsis (Milner et al., 2013). AtZIP1 is a transporter localized to the tonoplast and probably involved in remobilizing Mn^{2+} from vacuoles to the cytosol in root stele cells, whereas AtZIP2 is localized to the plasma membrane and may mediate Mn^{2+} uptake into cells of the root stele. Other Mn^{2+} transporters of the AtZIP family are also expressed in roots, but their function in Mn^{2+} uptake and remobilization is still unknown (Milner et al., 2013).

In comparison with other plant species, in rice, transporters involved in uptake, xylem loading, and root-to-shoot translocation of Mn have been functionally characterized more extensively (Shao et al., 2017). The first Mn^{2+} transporter identified in rice roots was OsNRAMP5, which contributes to Mn^{2+} uptake and translocation (Sasaki et al., 2012). Further investigations showed that Mn^{2+} uptake and translocation works in conjunction with another transporter next to OsNRAMP5,

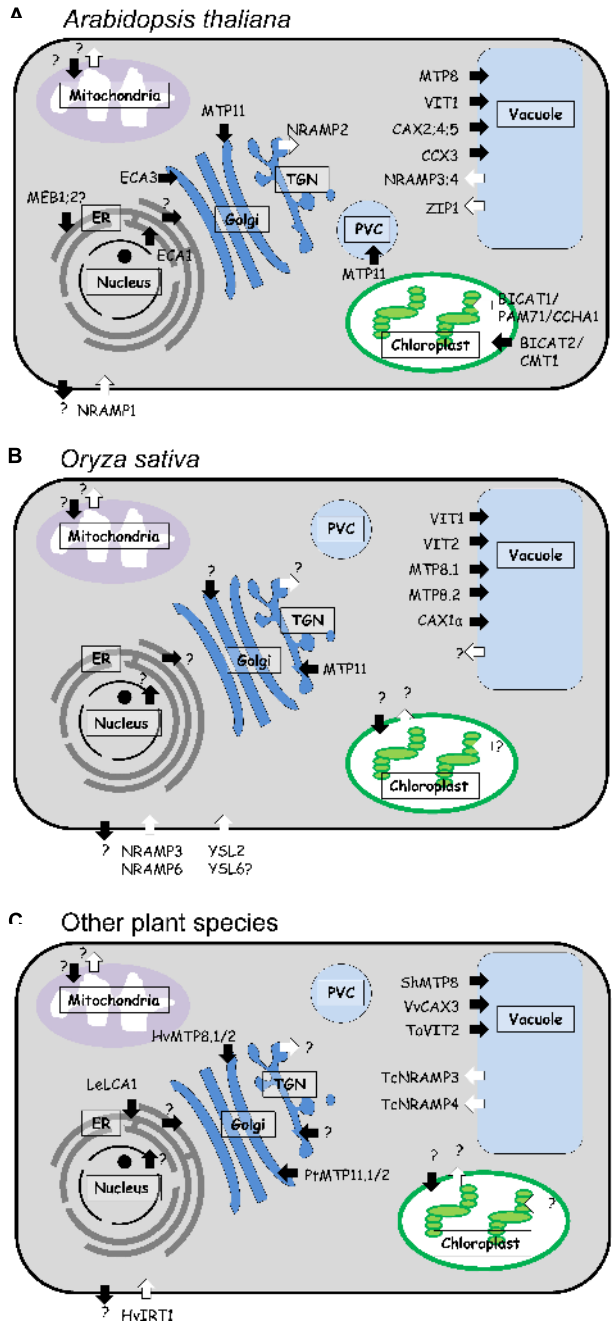

FIGURE 3 | Subcellular localization of Mn transport proteins in aerial parts of different plant species. **(A)** Arabidopsis, **(B)** rice, and **(C)** other species. White arrows represent import into the cytosol, black arrows represent export from the cytosol. Transport pathways with uncharacterized Mn transporters are indicated by a question mark. Hv, *Hordeum vulgare*; Le, *Lycopersicum esculentum* (syn. *Solanum lycopersicum*); Pt, *Populus trichocarpa*; Sh, *Stylosanthes hamata*; Ta, *Triticum aestivum*; Vv, *Vitis vinifera*.

namely OsMTP9 (Ueno et al., 2015). OsNRAMP5, localized to the plasma membrane of the distal side of the exo- and endodermis was shown to be responsible for the import of Mn^{2+} from the soil solution (**Figure 1B**). Subsequently, OsMTP9, localized to the plasma membrane of the proximal side of these cell layers, mediates the export of Mn^{2+} into the stele (Sasaki et al., 2012; Ueno et al., 2015). Knockout of either *OsMTP9* or *OsNRAMP5* significantly decreased Mn^{2+} uptake and root-to-shoot translocation, indicating that both transporters are responsible for transporting Mn^{2+} from the soil to the xylem.

Interestingly, in barley, the plasma membrane transporter HvIRT1 is implicated in the uptake and translocation of Mn^{2+}, but not Fe^{2+} (Long et al., 2018). *HvIRT1* is constitutively expressed in cells of the epidermis and in pericycle funder cells (**Figure 1C**), but under Mn deficiency, its expression is extended to the entire pericycle and the cortex. In *hvirt1* RNAi lines, a reduced shoot Mn concentration was observed without changes in Fe or Zn concentrations. Barley is characterized as a strategy II plant species that requires HvYSL transporters for the uptake of Fe^{3+} complexed with phytosiderophores (PS) (Araki et al., 2011). Therefore, the Fe transport function of HvIRT1 has become redundant because Fe is acquired via strategy II processes. Although HvIRT1 may transport Fe in yeast (Pedas et al., 2008), HvIRT1 plays actually a key role in uptake and root-to-shoot translocation of Mn rather than Fe. HvNRAMP5 is another Mn transporter localized to the plasma membranes of cells in root tips of barley (Wu et al., 2016). In contrast to *HvIRT1*, its expression is slightly upregulated by Fe deficiency, but not by Mn deficiency. Since *HvIRT1* is up-regulated by Mn deficiency and *HvNRAMP5* is constitutively expressed in roots (Wu et al., 2016), both transporters may play different roles. Therefore, it has been suggested that HvNRAMP5 may confer constitutive Mn^{2+} uptake, while HvIRT1 plays a role in Mn^{2+} uptake only under Mn-deficient conditions (Wu et al., 2016). The barley transporter HvYSL2 appears to mediate the transport of PS complexes with metals, including Mn, in the endodermis, and it may thus be involved in the transport of minerals from the cortex to the pericycle (Araki et al., 2011). However, further analyses of HvYSL2 are required to fully understand its biological role in barley.

Once Mn has been absorbed by the root, it needs to be translocated to the shoot. To date, the molecular basis of xylem loading of Mn is still unclear, and there is no clear evidence of which Mn complex is required to translocate Mn to the shoot via the xylem. Nevertheless, transporters of the YSL family may be involved in Mn translocation. In fact, during senescence, Mn concentration decreased in Arabidopsis wild type leaves, whereas no change was observed in the *ysl1ysl3* double mutant (Waters et al., 2006). Hence, it has been proposed that both AtYSL1 and AtYSL3 are putative Mn-nicotianamine (Mn^{2+}-NA) transporters, but so far, there is no direct evidence supporting this hypothesis. In rice, Mn^{2+} is transferred by OsNRAMP3 from the xylem to the phloem at the basal node, followed by its distribution to young leaves, panicles and root tips (Yamaji et al., 2013). However, at high Mn availability, Mn is distributed to mature tissues. Therefore, in rice nodes OsNRAMP3 functions as a switch for Mn distribution, whereby the protein is activated or deactivated in response to fluctuating Mn concentrations (**Figure 2B**). Moreover, a rice YSL transporter, OsYSL2, was proposed to be implicated in long-distance transport and distribution of Mn, since it may transport Mn^{2+}-NA, as well

as Fe^{2+}-NA complexes (Koike et al., 2004). Because OsYSL2 is localized in phloem companion cells, it is probably involved in phloem loading of Mn^{2+}-NA (Ishimaru et al., 2010), although its exact role in rice needs to be further investigated.

MANGANESE UPTAKE BY LEAF CELLS

As described above, a number of plasma membrane transporters involved in Mn^{2+} import into the cytosol of root cells has been characterized. In contrast, the identity of Mn^{2+} transporters in the plasma membrane of leaf cells remains largely elusive. Recently, it has been reported that OsNRAMP6, which is expressed in shoots, is localized to the plasma membrane (**Figure 3B**) and functions as Fe and Mn^{2+} transporter when expressed in yeast (Peris-Peris et al., 2017). Interestingly, OsNRAMP6 rescued, to some extent, the growth of yeast strains mutated in *SMF1* (plasma membrane Mn^{2+} transporter) or *SMF2* (Mn^{2+} transporter in intracellular vesicles) under Mn-limited conditions. In plants, OsNRAMP6 accumulated in vesicles in the vicinity of the plasma membrane. Whether these vesicles represent an anterograde or retrograde trafficking stage of OsNRAMP6, depending on the Mn^{2+} status, remains to be elucidated. Moreover, an *OsNRAMP6* knock-out plant showed enhanced resistance to infection by the rice fungus *M. oryzae* and a reduced biomass compared to wild type plants (Peris-Peris et al., 2017). Therefore, it is likely that OsNRAMP6 plays a role in regulating the Mn and/or Fe contents in infected tissues which would boost the expression of defense genes. Based on the decreased root and shoot biomass of the *nramp6* mutant under non-stress conditions, it was hypothesized that OsNRAMP6 functions as a Mn uptake transporter. Future studies are needed to establish the importance of OsNRAMP6 in cellular Mn^{2+} uptake and plant growth.

A second mechanism for Mn uptake into leaf cells of rice may be conferred by the OsYSL6 transporter, which was described to transport Mn^{2+}-NA complexes from the leaf apoplast to the symplast (Sasaki et al., 2011). *OsYSL6* is expressed in roots and shoots, particularly in older leaves. Due to the ability of OsYSL6 to increase Mn^{2+} influx when expressed in the *smf1* yeast mutant, it is likely localized in the plasma membrane (Sasaki et al., 2011). *ysl6* mutant plants accumulate high Mn concentrations in the apoplast of shoots and exhibit symptoms of Mn toxicity. Therefore, it is likely that OsYSL6 translocates Mn^{2+} from the apoplast to the symplast where it is sequestered under Mn excess. However, since its expression level remains unchanged under either Mn deficiency or excess, OsYSL6 may also act as a constitutive Mn importer in leaf cells.

INTRACELLULAR TRANSPORT OF MANGANESE

Once Mn has entered a plant cell, it must be moved to the appropriate location for the adequate supply of Mn-dependent targets or for storage. Mn is present in all cellular compartments, including ER, Golgi apparatus, mitochondria, plastids, and peroxisomes, where it performs specific cellular functions (see section Functions of Manganese in Plants), whereas vacuoles can serve as a reservoir to regulate cellular Mn homeostasis. Consequently, cells contain a plethora of transporters that are responsible for the distribution of Mn to the different compartments. **Figure 3** shows an overview of Mn transporters previously described in different plant species and their subcellular localization. To structure the description of these Mn transporters in the following sections, they are organized based on their demonstrated or putative subcellular localization.

Vacuoles as Manganese Stores

Vacuoles generally function as a primary compartment for metal internalization to avoid metal toxicity. In the case of Mn, vacuoles also serve as a temporal Mn storage pool for a proper distribution to other organelles, e.g., chloroplasts (Lanquar et al., 2010). Many transporters have been described to contribute to vacuolar Mn sequestration and unloading processes.

In the tropical legume *Stylosanthes hamata*, a plant tolerant to acidic soils in which high concentrations of plant-available Mn^{2+} can occur, the tonoplast-localized Mn transporter ShMTP8 was identified (Delhaize et al., 2003). This protein was the first characterized member of the Mn-CDF subgroup and is involved in Mn detoxification by sequestering Mn into vacuoles. Sequence analysis of *ShMTP8* showed that this protein lacks the complete N-terminal sequence and the histidine-rich loop common for members of the CDF family. When expressed in Arabidopsis, *ShMTP8* conferred tolerance to Mn toxicity (Delhaize et al., 2003). In pear and tobacco, members of the Mn-CDF subclade have also been described as Mn transporters, but their subcellular localization and relevance in Mn homeostasis is unknown (Hou et al., 2019; Liu et al., 2019). In Arabidopsis, the Mn-CDF subclade of the CDF/MTP family has four members, AtMTP8 through AtMTP11 (Montanini et al., 2007). All of them were shown to transport Mn^{2+} in yeast (Chu et al., 2017), but so far, only *AtMTP8* and *AtMTP11* have been described in more detail (**Figure 3A**). AtMTP8 was characterized as Mn^{2+} and Fe^{2+} transporter localized in the tonoplast (Eroglu et al., 2016; Chu et al., 2017; Eroglu et al., 2017). *AtMTP8* expression was specific to cells of the epidermis and the cortex in roots and strongly induced by Fe deficiency (Eroglu et al., 2016). Moreover, *mtp8* mutants showed chlorosis and critically low Fe levels in shoots on media with limited Fe availability, if Mn was present in the medium. This further demonstrated a Mn-specific role of AtMTP8 during Fe limitation, which lies in the detoxification of Mn taken up by the non-specific Fe transporter AtIRT1. In accord with a function of AtMTP8 in Mn detoxification, growth of *mtp8* mutants was impaired by high Mn, and *AtMTP8* expression was increased under excess Mn^{2+} supply (Eroglu et al., 2016). Besides its role in the Fe deficiency response, AtMTP8 plays a second role during seed development. An analysis of metal localization in the embryo by μXRF tomography showed that AtMTP8 is responsible for the specific accumulation of Mn in subepidermal cells on the abaxial side of the cotyledons and in cortical cells of the hypocotyl (Chu et al., 2017; Eroglu et al., 2017). In mutant embryos lacking the vacuolar Fe/Mn transporter AtVIT1, AtMTP8 built up Fe hotspots in those *AtMTP8*-expressing

cell types, suggesting that AtMTP8 transports Fe in addition to Mn. This was supported by complementation of the Fe-sensitive yeast strain *ccc1*. An *mtp8vit1* double mutant showed a homogeneous distribution of both metals in all cell types of the embryo, demonstrating that both are the primary transporters determining Mn and Fe allocation (Chu et al., 2017; Eroglu et al., 2017). Mn^{2+} transport and vacuolar localization were also demonstrated for MTP8 orthologs in rice (**Figure 3B**). *OsMTP8.1* was highly expressed in older leaves, and it was induced and repressed by high and low Mn^{2+} levels, respectively (Chen et al., 2013). *OsMTP8.2* was expressed in roots and shoots, and it showed lower expression levels than *OsMTP8.1* (Takemoto et al., 2017). The *mtp8.1mtp8.2* double mutant suffered from necrotic leaf blades. Since Mn concentrations were comparable to those in healthy wild type plants, it has been suggested that this phenotype was the result of an insufficient Mn sequestration in the double mutant. Unlike AtMTP8 in Arabidopsis, there is no evidence that OsMTP8.1 and OsMTP8.2 are able to transport Fe or that their transcript levels are increased upon Fe deficiency (Chen et al., 2013; Takemoto et al., 2017).

VIT proteins in plants are mainly Fe transporters (Cao, 2019). AtVIT1, the most-studied VIT transporter in Arabidopsis, was identified as a vacuolar Fe transporter that is responsible for the localization of Fe primarily to the provascular strands of the embryo in seeds (Kim et al., 2006). The ability of AtVIT1 to transport Mn^{2+} was shown by metal analysis of vacuoles from the Fe-sensitive yeast strain *ccc1* expressing *AtVIT1* (Kim et al., 2006). Interestingly, seeds of a *vit1* mutant showed a localization of Fe that coincided with the localization of Mn in the subepidermal cells on the abaxial side of the cotyledons and that was dependent on AtMTP8, as discussed above (Chu et al., 2017; Eroglu et al., 2017). VIT transporters of rice, OsVIT1 and OsVIT2, not only partially rescued the Fe^{2+}-sensitive phenotype, but also the Zn^{2+}-sensitive phenotypes of yeast mutant strains. Similar to AtVIT1, an analysis of vacuolar metal composition of these cells showed an increased accumulation of Mn (Zhang et al., 2012). Moreover, *OsVIT1* and *OsVIT2* were shown to be highly expressed in flag leaf blades and leaf sheath. Consistent with these results, decreased accumulation of Fe and Zn was observed in flag leaves of *osvit1* and *osvit2* mutants. However, both mutants showed no significant change of Mn in these tissues or in grains (Zhang et al., 2012). These results suggest that OsVIT1 and OsVIT2 may function primarily in flag leaves to mediate vacuolar sequestration of Fe and Zn. Moreover, the Fe and Zn accumulation in seeds and the decrease of those metals in flag leaves (the source organ) of *osvit1* and *osvit2* mutants indicates an indirect involvement of both gene products in translocation of both metals to sink organs, since they are only weakly expressed in embryos, which is in contrast to *AtVIT1* (Zhang et al., 2012). Finally, there are two VIT homologs in wheat, which are located to the tonoplast (**Figure 3C**), but only one of them, namely TaVIT2, was shown to complement a Mn-sensitive yeast strain, *pmr1*. TaVIT2 was also able to transport Fe^{2+} and has been employed for biofortification of wheat grains with Fe (Connorton et al., 2017).

Members of the CAX family are metal transporters that mediate efflux of cations into the vacuole (Martinoia et al., 2012). All plant CAX transporters characterized to date appear to be able to transport Ca^{2+}. Nevertheless, a broad metal substrate range, including Mn^{2+}, is a common characteristic of these proteins. Based on amino acid sequences, the plant CAX family is divided into two clusters, type 1-A and 1-B. Their capability to transport Mn^{2+} is not related to their phylogenetic association, with *AtCAX4*, *OsCAX1a*, and *VvCAX3* being members of the type 1-A subfamily and *AtCAX2*, *AtCAX5*, *OsCAX3*, and *OsCAX4* being members of the type 1-B subfamily (Martins et al., 2017). AtCAX2 transports a range of cations into the vacuole, including Mn^{2+}, Zn^{2+}, and Cd^{2+} (Koren'kov et al., 2007). Knockout analysis suggested that AtCAX2 does not play a major physiological role in Ca homeostasis, but is more important for vacuolar Mn accumulation (Pittman et al., 2004). However, vacuolar Mn^{2+} transport was not completely abolished in *cax2*. AtCAX5 is a likely candidate for this residual activity. AtCAX5 showed a lower Ca^{2+} and Mn^{2+} transport activity than AtCAX2 as also a reduced Ca^{2+} transport capacity (Edmond et al., 2009). Despite the significant sequence similarity and substrate specificity of AtCAX2 and AtCAX5, a clear distinction appeared in their expression pattern and transcriptional regulation. *AtCAX5* was expressed in all tissues of Arabidopsis seedlings, particularly in the stem and the root, and at a lower level in the leaf. In addition, there was an increase in *AtCAX5* transcripts under conditions of excess Mn, and a reduction in response to excess Zn. In contrast, *AtCAX2* was detected at fairly low levels in all tissues, but was not greatly induced by any metal (Edmond et al., 2009). The relevance of these CAX transporters in intracellular Mn homeostasis is unclear. Since only the Arabidopsis *cax2* mutant showed a growth defect under Mn deficiency (Connorton et al., 2012), future genetic analysis by using *cax2cax5* double mutant plants may uncover the physiological function of these transporters in plants.

CAX2-like transporters of other species, as tomato LeCAX2 and barley HvCAX2, transport Ca^{2+} and Mn^{2+} into yeast vacuoles upon heterologous expression, but with different transport kinetics (Edmond et al., 2009). *HvCAX2* is expressed ubiquitously in roots, shoot, immature spikes, and in seeds, preferentially in the embryo rather than the endosperm. Transcripts of *HvCAX2* increased under excess Ca^{2+} and Na^{+}. Likewise, *LeCAX2* was also expressed in roots and to a higher extend in leaves and fruits (Edmond et al., 2009).

AtCAX4 was expressed at low level in all tissues, and expression increased after Mn^{2+}, Na^{+}, and Ni^{2+} treatment (Cheng et al., 2002). Specifically, *AtCAX4* transcript levels increased in the root apex and lateral root primordia upon Mn^{2+} and Ni^{2+} treatment and decreased if Ca^{2+} was depleted. Mutation of *AtCAX4* led to an arrested growth in seedlings under excess Cd^{2+}, Mn^{2+}, and auxin (Mei et al., 2009). Previously, a link between auxin-regulated plant development, cytosolic Ca^{2+}, and kinases was described (Robert and Offringa, 2008). Therefore, these findings suggest that the *cax4* mutant may have increased cytosolic Ca^{2+} levels (because of reduced Ca^{2+} transport into the vacuole), that cause an impaired auxin gradient and altered root development (Mei et al., 2009). Alternatively, the auxin sensitivity phenotype may be a result of altered Mn homeostasis in *cax4* mutants, since Mn has an influence

on auxin responses and auxin metabolism (Mei et al., 2009). VvCAX3 is a ubiquitously expressed vacuolar transporter for both, monovalent and divalent cations in grapevine. Expression of *VvCAX3* in yeast restored the growth on media with high Na^+, Li^+, Cu^{2+}, and Mn^{2+} concentrations (Martins et al., 2017). Interestingly, expression of *VvCAX3* decreased during the development in parallel with Ca^{2+} accumulation in the fruit. It is likely that VvCAX3 is not only involved in Ca^{2+} sequestration, but also in the detoxification of trace elements and the mitigation of salt stress, since its transcript level increased under NaCl treatment (Martins et al., 2017).

Other members of the type 1-B subfamily of CAX transporters are *OsCAX3* and *OsCAX4* in rice. *OsCAX3* is expressed in all plant tissues, and the protein has a capacity to transport Mn^{2+}. Interestingly, when expressed in yeast, next to Mn tolerance *OsCAX3* also conferred Ca^{2+} tolerance, but to a lower extent compared to other OsCAX transporters. Therefore, OsCAX3, as AtCAX2, might preferentially transport Mn^{2+}, rather than Ca^{2+}, into the vacuole (Kamiya et al., 2005). Nevertheless, future work is needed to confirm its vacuolar localization. By contrast, expression of *OsCAX4* provides Mn and Cu tolerance to yeast, and *OsCAX4* transcripts were increased upon prolonged salt stress *in planta* (Yamada et al., 2014). A type 1-A transporter of rice, OsCAX1a, transports Ca^{2+} and Mn^{2+} into yeast vacuoles, but is involved mainly in Ca^{2+} homeostasis in plant cells under high concentrations of Ca^{2+} (Kamiya et al., 2006). Further analysis of the function of OsCAX1a *in planta* showed that the transcript level in roots was increased by Ca^{2+} and decreased by Mn^{2+}, Ni^{2+}, Mg^{2+}, and Cu^{2+}, while shoots showed only an increase of *OsCAX1a* transcript levels after treatment with Ca^{2+}. The decreased expression of *OsCAX1a* in response to other divalent cations might be a mechanism to keep high concentrations of cytosolic Ca^{2+} in order to protect the cell from toxic levels of ions like Mn^{2+} (Kamiya et al., 2006). Therefore, OsCAX1a may transport Ca^{2+} into the vacuole under Ca^{2+} toxicity or regulate Ca^{2+} homeostasis in the cytosol. In rice, further studies using combined mutants of *OsCAX1a*, *OsCAX3*, and *OsCAX4* are needed to confirm their relevance in plant Mn^{2+} and Ca^{2+} homeostasis.

Members of the CCX family were previously described as transporters of the CAX family. However, because they are phylogenetically closer to the mammalian plasma membrane K^+-dependent Na^+/Ca^{2+} exchangers (NCXs), this gene family, which has five members in Arabidopsis (CCX1-5), was re-classified (Pittman and Hirschi, 2016). Expression of *AtCCX3* was induced in roots and flowers upon treatment with Mn^{2+}, and in yeast the expression of *AtCCX3* complemented strains defective in Mn^{2+} export (Morris et al., 2008). Tobacco cells expressing *AtCCX3* showed enhanced Mn levels, further suggesting an ability of AtCCX3 to transport Mn^{2+}. The transcript level of *AtCCX3* increased in plants upon a treatment with Na^+, K^+, and Mn^{2+}, albeit a mutation in *AtCCX3* provoked no discernible growth abnormalities under those conditions (Morris et al., 2008).

The genome of Arabidopsis contains six genes encoding NRAMP transporters, whereby AtNRAMP3 and AtNRAMP4 have been localized to the tonoplast (Thomine et al., 2003; Lanquar et al., 2005). The NRAMP homologs TcNRAMP3 and TcNRAMP4 from *Thlaspi caerulescens* were also localized to the tonoplast (Oomen et al., 2009). These NRAMP transporters from both species are involved in the transport of Cd^{2+}, Fe^{2+}, and Mn^{2+} (Thomine et al., 2000; Oomen et al., 2009; Pottier et al., 2015). In addition, AtNRAMP4 and TcNRAMP4 also transport Zn^{2+} when expressed in yeast (Lanquar et al., 2004; Oomen et al., 2009; Pottier et al., 2015). AtNRAMP3 and AtNRAMP4 protein levels in leaves were unaffected by Mn deficiency, but expression of *AtNRAMP4* was induced under Fe-limited conditions (Lanquar et al., 2010). Both proteins were shown to be responsible for the retrieval of Fe from vacuoles during seed germination and to mediate the export of vacuolar Mn in photosynthetic tissues of adult plants (Lanquar et al., 2005, 2010). The *nramp3nramp4* double mutant had comparable Mn concentrations in leaf mesophyll cells as wild type plants, but it showed a strong accumulation of Mn in the vacuoles (Lanquar et al., 2010). Under Mn deficiency, the double mutant showed a decreased growth which was correlated with reduced photosynthetic activity as a consequence of a shortage of Mn for the formation of OEC complexes in PSII. In contrast, *nramp3nramp4* did not show altered mitochondrial MnSOD activity under Mn deficiency (Lanquar et al., 2010). These results suggest an important role for AtNRAMP3/AtNRAMP4-dependent Mn transit through the vacuole prior to the import into chloroplasts of mesophyll cells.

Manganese Accumulation in Chloroplasts

Mn plays an extremely important role in chloroplast function, as it is essential for photosynthetic activity. There is a high demand for Mn in the photosynthetic apparatus, mainly for the formation of the Mn_4Ca -cluster in the OEC of PSII, which is essential for water splitting. In spite of the importance of Mn for chloroplast function, only recent studies have reported the identification and characterization of Mn transporters in chloroplast membranes. Two members of the BICAT family, which are related to the GDT1 protein in yeast (Demaegd et al., 2013) and the Mnx protein in the cyanobacterium *Synechocystis* (Brandenburg et al., 2017), are involved in Mn loading of the chloroplast and the distribution within this organelle (**Figure 3A**).

The Arabidopsis AtBICAT1 (syn. PAM71, CCHA1) protein is localized in the thylakoid membrane and transports Ca^{2+} and Mn^{2+} into the thylakoid lumen (Schneider et al., 2016; Wang et al., 2016; Frank et al., 2019). AtBICAT1 complemented the Mn-sensitive phenotype of the *pmr1* yeast mutant and mediated Ca^{2+} influx upon expression in *E. coli*. *bicat1* knockout mutants showed slightly pale green leaves along with compromised growth. Interestingly, growth retardation and photosynthetic activity of *bicat1* could be partially restored by exogenous treatment with Mn^{2+} (Schneider et al., 2016). In addition, transient elevations of the stromal free Ca^{2+} concentration, induced by a light-to-dark shift, were increased in *bicat1* mutants (Frank et al., 2019). Based on these findings, AtBICAT1

presumably functions in Mn^{2+} and Ca^{2+} flux into thylakoids for assembly of the Mn_4Ca-cluster, and also in the homeostasis of stromal Ca^{2+}, which regulates numerous processes in chloroplasts (Sello et al., 2018).

AtBICAT2 (syn. PAM71HL, CMT1), the second member of this family, was also described to fulfill functions in chloroplast Mn and Ca^{2+} homeostasis (Eisenhut et al., 2018; Frank et al., 2019). In contrast to AtBICAT1, it resides in the chloroplast envelope. Like *AtBICAT1*, the expression of *AtBICAT2* can also alleviate the Mn^{2+} and Ca^{2+} sensitivity phenotypes of the *pmr1* and *pmr1gdt1* yeast mutants, respectively. Disruption of *AtBICAT2* resulted in strong chlorosis, severely impaired plant growth, defective thylakoid stacking, and severe reduction of PS II complexes, resulting in diminished photosynthetic activity (Eisenhut et al., 2018; Frank et al., 2019). Consistent with a reduced oxygen evolution capacity, *bicat2* mutant chloroplasts contained less Mn than those of the wild type (Zhang et al., 2018). Also, mutants were defective in Ca^{2+} uptake across the chloroplast envelope and showed a strongly dampened dark-induced Ca^{2+} signal in the stroma (Frank et al., 2019). As consequence, the disruption of *AtBICAT2* should also lead to a decreased Ca^{2+} import into the thylakoid lumen. Taken together, these results indicate that AtBICAT2 functions as an inner envelope transporter responsible for chloroplast Mn^{2+} and Ca^{2+} uptake. Ca^{2+} dynamics and Mn concentrations in both, stroma and lumen, were likely diminished in *bicat2* mutants, which may explain the stronger phenotype compared to that of *bicat1* mutants. The phenotype of *bicat1bicat2* double mutants suggest that *AtBICAT2* is the limiting step in Mn^{2+} and Ca^{2+} delivery to the chloroplast. Further work is needed to unravel the bi-functionality and regulation of BICATs in Ca^{2+} and Mn^{2+} homeostasis in chloroplasts.

Manganese Transport Proteins in Endomembranes

The Arabidopsis CDF protein AtMTP11 was shown to exhibit an important role in Mn detoxification. The promoter of *AtMTP11* had a high activity in root tips, shoot margins, and hydathodes, but not in epidermal cells and trichomes. Expression of *AtMTP11* in yeast complemented the Mn^{2+} hypersensitivity of the *pmr1* mutant (Peiter et al., 2007). In Arabidopsis, *mtp11* mutants were hypersensitive to elevated Mn^{2+} levels, whereas *AtMTP11*-overexpressing lines were hypertolerant (Delhaize et al., 2007; Peiter et al., 2007). As AtMTP11 appeared to be localized to the prevacuolar compartment (PVC) or to the Golgi apparatus (**Figure 3A**), it was suggested that it functions in the accumulation of excess Mn either into vacuoles via the PVC or in the secretion to the apoplastic space via vesicle-mediated exocytosis (Delhaize et al., 2007; Peiter et al., 2007). The latter pathway was supported by increased Mn concentrations in *mtp11* mutants (Peiter et al., 2007). Two poplar homologs of this protein, PtMTP11.1 and PtMTP11.2, were also able to complement the Mn-sensitive yeast mutant *pmr1* and targeted to the same Golgi compartments as AtMTP11 (**Figure 3C**; Peiter et al., 2007). Those genes are therefore likely to function in a similar way. Another MTP11 ortholog in rice, OsMTP11, was also described to be involved in Mn detoxification. *OsMTP11* is induced by high Mn and expressed specifically in conducting tissues (Zhang and Liu, 2017). Interestingly, epigenetic mechanisms (e.g., DNA methylation) were a major factor regulating the expression level of *OsMTP11* (Zhang and Liu, 2017). Knockdown of *OsMTP11* resulted in growth inhibition in the presence of high concentrations of Mn^{2+} and also led to increased accumulation of Mn in shoots and roots. By contrast, the overexpression of *OsMTP11* enhanced Mn tolerance of rice and decreased the accumulation of Mn in shoots and roots (Ma et al., 2018). Stable expression of *OsMTP11-GFP* in Arabidopsis and transient expression of this construct in rice and tobacco protoplasts showed that OsMTP11 was also located to the Golgi (**Figure 3B**; Farthing et al., 2017). However, recent studies suggested that OsMTP11 localized to the trans-Golgi network (TGN) when it was expressed in rice protoplasts and tobacco epidermal cells (Ma et al., 2018). Surprisingly, in tobacco epidermal cells, OsMTP11 relocalized to the plasma membrane upon treatment with high extracellular Mn^{2+} concentrations. These findings suggest that OsMTP11 is required for Mn homeostasis and contributes to Mn^{2+} tolerance in rice (Ma et al., 2018).

In the sugar beet relative *B. vulgaris* spp. *maritima*, the MTP11 homologs BmMTP10 and BmMTP11 were also characterized as Mn^{2+} transporters by complementation of the *pmr1* yeast strain (Erbasol et al., 2013). In barley, transient expression in onion epidermal cells showed that the HvMTP8.1 and HvMTP8.2 proteins, which are most closely related to the vacuolar AtMTP8 (see section Vacuoles as Manganese Stores), were localized to the Golgi apparatus and also complemented the *pmr1* strain (Pedas et al., 2014). However, the function of those CDF proteins *in planta* is still unclear.

The Arabidopsis genome encodes 15 P-type Ca^{2+}-ATPases, of which the P_{2A} -type or ECA (ER-type Calcium ATPase) subfamily has two members involved in endomembrane Mn^{2+} transport (Kamrul Huda et al., 2013). AtECA1 and AtECA3 both function as a pump for Ca^{2+} and Mn^{2+}, and localize to the ER and Golgi apparatus, respectively (**Figure 3A**). Furthermore, AtECA3 was shown to be localized also in subpopulations of endosomes or PVC (Li et al., 2008). *AtECA1* and *AtECA3* expression in the K616 yeast mutant, defective in the Golgi Ca^{2+} and Mn^{2+} pump PMR1 and in the vacuolar Ca^{2+} pump PMC1, increased its tolerance to toxic levels of Mn^{2+} and to Ca^{2+} deficiency (Liang et al., 1997; Wu et al., 2002; Mills et al., 2007). Another ER-localized ECA transporter in tomato, LCA1, also complemented the growth of K616 yeast under conditions of high Mn^{2+} and low Ca^{2+} (Johnson et al., 2009). *eca1* mutants of Arabidopsis showed impaired growth under Ca^{2+} deprivation and Mn^{2+} excess. On high-Mn^{2+} media, root hair elongation was inhibited in the mutants, suggesting an impairment in tip growth (Wu et al., 2002). Taken together, AtECA1 and LeLCA1 are likely involved in the transport of Ca^{2+} and Mn^{2+} from the cytosol into the ER. On the other hand, *eca3* was shown to be sensitive to Mn deficiency and also to Mn toxicity, but not to Ca^{2+} deficiency (Mills et al., 2007; Li et al., 2008). Thus, the phenotype of *eca3*, observed under Mn-deficient conditions, may be due

to a reduction of the Mn content in the Golgi. Based on these studies, CDF and ECA proteins may be responsible for Mn^{2+} loading of Golgi-related vesicular compartments, for delivering Mn to Mn-dependent enzymes and/or for detoxification of Mn via a secretory pathway.

In Arabidopsis, AtNRAMP2 is located in the TGN (**Figure 3A**) and was shown to be involved in the intracellular allocation of Mn (Alejandro et al., 2017; Gao et al., 2018). *AtNRAMP2* is mainly expressed in the vasculature of roots and shoots and was barely induced upon Mn deficiency. Nevertheless, *nramp2* mutants showed a hypersensitivity to Mn deficiency and a reduction in Mn contents in vacuoles and chloroplasts with an accompanying reduction in PSII activity under those conditions (Alejandro et al., 2017). Surprisingly, the *nramp2nramp3nramp4* triple mutant did not exhibit higher sensitivity to Mn deficiency than the single *nramp2* and double *nramp3nramp4* mutants (Alejandro et al., 2017). This suggests that the three transporters act in the same pathway to deliver Mn to the chloroplasts.

NRAMP transporters from tomato (LeNRAMP1 and LeNRAMP3) and apple (MbNRAMP1) were also able to transport Mn^{2+} and located to intracellular vesicles when expressed in yeast cells, but their function in Mn homeostasis is still unclear (Bereczky et al., 2003; Xiao et al., 2008).

ER bodies are fusiform compartments connected to the ER that were found specifically in Brassicales (Matsushima et al., 2003). It has been proposed that ER bodies might play a role in the defense against pathogens and herbivores (Yamada et al., 2011). In Arabidopsis, two VIT transporters, AtMEB1 (Membrane protein of Endoplasmic reticulum Body) and AtMEB2, that localize to the ER body membrane but not to the ER network, have been identified (Yamada et al., 2013). Heterologous expression of *AtMEB1* and *AtMEB2* in yeast suppressed Fe and Mn toxicity, suggesting that they possibly act as metal transporters. ER bodies are present in hypocotyls of seedlings where they disappear during plant development. In contrast, in roots, ER bodies are constitutively present. Therefore, it has been suggested that MEB transporters may be involved in the sequestration of metals into root ER bodies under metal stress conditions (Yamada et al., 2013).

Manganese Homeostasis in Other Organelles

In mitochondria, Mn is crucial for the activity of MnSOD which scavenges ROS generated within the citric acid cycle and the electron transport chain. However, the transport mechanisms for Mn^{2+} in plant mitochondria still remain to be elucidated. To date, no transporter involved in Mn^{2+} transport to and from plant mitochondria has been characterized. Nevertheless, in humans, a mitochondrial Ca^{2+} uniporter (MCU) that is responsible for Ca^{2+} and Mn^{2+} loading into the mitochondria has been described (Kirichok et al., 2004). Arabidopsis has six MCU isoforms which are predicted to be localized in mitochondria, except one, cMCU, that is targeted to the chloroplast (Stael et al., 2012). The cMCU protein mediates Ca^{2+} fluxes across the chloroplast envelope (Teardo et al., 2019). In humans, MCU is part of a complex named MCUC (MCU complex) which includes other subunits, including the EF hand-containing proteins MICU1 and MICU2 (Ca^{2+}-sensing inhibitory subunit). MICU1 plays a decisive role in ion specificity of MCU, allowing it to distinguish between Ca^{2+} vs. Mn^{2+} (Kamer et al., 2018). In Arabidopsis, a MICU homolog, AtMICU, that binds Ca^{2+} and localizes to the mitochondria, was described (Wagner et al., 2015). These findings provoke the idea that a conserved uniporter system, similar to MCUC in humans, may mediate Ca^{2+} and Mn^{2+} uptake by plant mitochondria.

In peroxisomes, Mn is important as a cofactor of the peroxisomal MnSOD. This enzyme is present in some plant species, including pea, cucumber, and pepper (Corpas et al., 2017). However, so far, transporters to load Mn into the peroxisomes are still missing.

CONCLUSION AND PERSPECTIVES

The relevance of manganese as a micronutrient of plants is still largely underestimated. For a long time, the accepted dogma among animal and plant biologists has been that the physiological requirement for Mn by living cells is low and that Mn uptake exceeds the requirement. However, in natural and in agricultural settings, Mn availability can be a seriously limiting factor for plant growth, which necessitates the operation of high-affinity Mn transporters in roots and efficient mechanisms of Mn distribution in the plant to cope with Mn shortage. Crops with improved Mn uptake capacity and Mn use efficiency will achieve higher growth and yield under suboptimal Mn availability, primarily by providing sufficient Mn to PSII and thus increasing their photosynthetic efficiency.

There are many unresolved issues in our understanding of Mn transport and homeostasis, such as the transport of Mn into the xylem – Is it mediated by a vesicle-based secretory mechanism or by plasma membrane-bound exporters? How Mn is imported by different cell types in the shoot is another open question. Most Mn^{2+} transporters are not specific, but also able to move other divalent cations, like Ca^{2+}, Fe^{2+}, Zn^{2+}, or Cu^{2+}, but so far it is still unclear if and how they discriminate between the cations. In humans, the substrate selectivity of a mitochondrial Mn transporter is altered by interacting EF hand proteins (Kamer et al., 2018). In this respect, the ability of diverse Ca^{2+} transport proteins to also permeate Mn^{2+} (or vice versa) is particular interesting. The possibility that Ca^{2+} and Mn^{2+} share transport pathways mediated by ECAs, BICATs, CAXs, and Ca^{2+} channels, implies an interference of Mn^{2+} in Ca^{2+} signaling. In fact, Mn^{2+} has been demonstrated to act as a signaling agent *per se* in humans (Wang et al., 2018).

The sensing and signaling of the plant's Mn status is another area yet to be explored: On which level is Mn transport activity regulated by the nutritional status of the plant? This review pointed out some transcriptional changes of Mn transporter-encoding genes under Mn-toxic and Mn-deficient conditions, but the signaling networks that underlie these changes are still missing. Furthermore, a

recent systems-wide analysis indicated that Mn deficiency responses are primarily regulated at the posttranscriptional level (Rodríguez-Celma et al., 2016). Moreover, our understanding of how Mn transport proteins are regulated is very rudimentary. In this respect, a couple of proteins that regulate the subcellular localization of AtNRAMP1 have been identified, revealing links to inositol phosphate and choline homeostasis (Agorio et al., 2017; Gao et al., 2017). As another fascinating case, it has been demonstrated that phosphorylation, ubiquitination, and metal binding modify the stability and localization of AtIRT1, an Fe^{2+} transporter that contributes to the uptake of Mn^{2+} (Dubeaux et al., 2018). However, for the vast majority of Mn transporters, posttranslational modifications and protein-protein interactions are unknown.

Future research has to be focused on all these fundamental aspects. The function, regulation, and co-operation of Mn^{2+} transport proteins in different plant tissues upon Mn deficiency and excess ought to be understood at transcriptional and at protein level. Such studies will eventually elucidate the mechanisms controlling Mn acquisition, subcellular compartmentation, and homeostasis in plants, a knowledge that can be harnessed to develop Mn-efficient germplasm of staple crops.

AUTHOR CONTRIBUTIONS

SA, SH, and BM drafted the manuscript. SA, SH, BM, and EP finalized the manuscript, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

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