The Copper Transport Mechanism in Plants

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Abstract

Heavy metals are required by plants in trace amounts for adequate growth and development, and their absence may lead to several detrimental effects during plant growth and development. Among them, one of the imperative trace elements required by plants for normal growth and development is copper. Copper (Cu) also serves as an important cofactor of many proteins. However, the details regarding these many Cu proteins are certainly limited. Nonetheless, the role played by these Cu proteins is of paramount significance. Cu holds an indispensable position in this regard; nevertheless, if its amount surpasses the required limit, it can lead to serious repercussions. Therefore, in order to maintain such a delicate balance, there exists an innate system within plants, which controls its absorption, distribution, and excretion within plants. There exists a unique set of proteins within plants termed as transport proteins, which regulate this delicate balance within plants. In the upcoming discussion, three of the most significant transport proteins also known as transporters are brought to light. These transport proteins include P type ATPases, that are responsible for the transport of Cu ions across the cell membrane, COPT proteins, that are responsible for the transport of Cu ions to various different cellular compartments, and chaperones that do not actually contain Cu but work like others, which are possessed with Cu. NRamp family gene analysis in soyabean seedlings also

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K. Kumar, S. Srivastava (eds.), *Plant Metal and Metalloid Transporters*,
https://doi.org/10.1007/978-981-19-6103-8_13

revealed their role during Cu and other heavy metal strain. The expression of this gene family also gets altered during heavy metal toxicity. The role of SPL7 transcription factor, in Cu homeostasis, has also been highlighted. In addition to it, the related role of Cu transport systems in biosynthesis and homeostasis has also been discussed.

Keywords

Copper · Copper response regulator · Homeostasis · COPT · NRAMP

Abbreviations

ATP	Adenosine triphosphate
Cu	Copper
CR	Copper response regulator
N ramp	Natural resistance-associated macrophage protein
ROS	Reactive oxygen species

13.1 Introduction

Plants, in addition to light and water, also require certain metal elements, in small amounts, which ensure apposite growth and development. Such elements are obtained either from the soil or from foliar applications (Yruela 2009). To draw these elements from soil in highly calculated way, plants have undergone evolution and, as a consequence of it, have evolved structures and ways to get to these mineral elements and also to ensure its efficient distribution. Presently, 17 elements are regarded by biologists as essential. Depending upon their required concentration, they are termed as micronutrients or macronutrients. If the required concentration of the mineral is below 100 mg/kg DW, the required minerals will be categorized as micronutrients, and if the required concentration of the mineral is above 1000 mg/kg DW, they are termed as macronutrients (Printz et al. 2016). To make it possible, plants have successfully evolved an in-built set of transporter proteins, channels, and pumps. These innate devices within plants help plant to not only absorb but also transfer and distribute minerals as per requirements. In reduced suitability of Fe during various physiological developmental stages, Cu serves as a strong alternative (Burkhead et al. 2009). In general, Cu occurrence is 60 mg/kg, and in European environment, its range is between 11.4 and 17 mg/kg (Alloway 2013).

Copper (Cu) is a vital element—a micronutrient, which is required by plants in minuscule amounts, for its proper growth and development. It is an important transition metal active in redox reaction, which carries many plants physiological processes as it can present in several oxidation states (Yruela 2005). The major functions performed by copper include its contribution in electron transport chain vital for both linked with photosynthesis and respiration. It also aids plants in sensing ethylene, metabolism occurring in cell wall, protection against oxidative stress, and synthesis of molybdenum cofactor (Yruela 2009). The significance of copper in plants' life cannot be overlooked.

Nevertheless, if the amount of Cu exceeds compared to the bare minimum of it being required, it can lead to plant damage and deterioration. It not only hampers the regular plant growth but also negatively affects the regular cellular processes occurring in the cells. Several studies have mentioned the negative effects as a result of excessive amounts of Cu on plant germination and growth, photosynthetic activity, and antioxidant response in case of several agricultural crops. The inhibition of mineral nutrition, biosynthesis of chlorophyll, and activity of antioxidant enzymes have been proved (Mir et al. 2021). Therefore, it can cause both damage and deterioration simultaneously. Such an increased concentration of Cu in the soil leading to higher levels of toxicity may occur when Cu becomes rich in parental materials, and pH of soil promotes metal availability, or soil pollution occurs by mining activities and waste deposits, or through intensive usage of plant disease control Cu-containing chemicals in agricultural, or rigorous use of manure or sewage sludge (Rehman et al. 2019; Kumar et al. 2021). For most of the crops, the serious toxicity level is over 20–30 mg/kg leaf dry weight, whereas in metallophytes tolerant to Cu, leaves may possess around 1000 μg/g leaf dry weight (Kupper et al. 2009; Monni et al. 2000).

However, as mentioned earlier, its absence can also have negative effects on growth and development of plants. The dearth of copper causes alterations in the expression of genes and also exhibit several deficiency symptoms in plant parts such as leave structure that gets distorted. The leaves first turn yellow, which can even lead to tissue death (Marschner 1995). Hence, its appropriate amount is required by plants to ensure proper growth and development. This indicates that, in plants, there exists a well-established mechanism of metal uptake by the roots from the soil and also for its translocation and distribution in all the required parts of plants. The maintenance of their concentration in the cytosol is indispensable for normal plant growth and development. To regulate these complicated and intricate processes, different transport proteins present within plants play their role.

Biochemical and molecular techniques have already helped scientists to understand these processes and will help further to explore ways to grow plants in heavy metal-contaminated zones, by developing varieties of plants, which will not absorb Cu heavy metals beyond requirement or will be able to get hold on them by developing in them both efficient and effective efflux, compartmentalization, or detoxification mechanism in response to its absorption besides requirement. Phytoremediation gained momentum to deal with the issue of soil contaminated with heavy metal (Salt et al. 1998). In the upcoming section, the transport mechanism of this indispensable metal in plants will be elucidated.

13.2 Mechanism of Copper (Cu) Transport in Plants

The importance of copper (Cu) in plants cannot be denied, however its excess can have repercussions is an established fact too. This suggests that there exists an in-built machinery that regulates the adequate transport of copper in plants. This further suggests that the device present in it is both delicate and sophisticated, which ensures regulated transport of copper in plants. However, the research on it was really limited, until research was conducted in which the transport processes in yeast and various other eukaryotic organisms were published (Nevo and Nelson 2006).

Under physiological circumstances, Cu exists in two forms, the reduced and oxidized Cu states as Cu I and Cu II, respectively. This dual nature helps it to bind with a variety of substrates (Cohu and Pilon 2010). This dual nature facilitates it to make bonds with diverse group of molecules prominently proteins, not only to run biochemical reactions but also to maintain structural ensembles (Festa and Thiele 2011). Nevertheless, redox Cu has the potential to produce reactive oxygen species (ROS) via a popular method called Fenton reaction, thereby damaging the proteins, DNA, and other biological molecules (Hänsch and Mendel 2009).

Cu homeostasis in plants is mediated by SPL7, Cu-responsive transcription factor. This SPL7 is regarded as a functional homolog of Cu response regulator 1 (CR1), which has semblance with SBP domain transcription factor that has been found in signaling of Cu in *Chlamydomonas reinhardtii* (Yamasaki et al. 2004; Kropat et al. 2005; Sommer et al. 2010). These SBP domains appear to be highly conserved domains for DNA binding and able to identify the TNCGTACAA site and particularly the GTAC core sequence (Printz et al. 2016). In plants, direct interaction between Cu and SPL7 is still not evident. However, it has been hypothesized that under sufficient Cu conditions, SPL7 may attach with Cu via specific Cu-complexes interactions, and this results in the lack of SPL7 ability to join the GTAC motif in the promotor of target genes (Garcia-Molina et al. 2014). This significant aspect of SPL7 regulation of Cu homeostasis needs further research. The research studies exhibited that there are several components, which are responsible for both efficient and effective Cu transport machinery. The different components of Cu transport machinery will be discussed in this chapter.

13.3 P-Type ATPase Copper Transporters

P-type ATPases have been reported in various different organisms that are meant to transport heavy metals across the plasma membrane. These heavy metals are both beneficial and harmful for plants, and this is basically dependent on the amount of it being present in the plant cell. P-type ATPases are a large superfamily that has subgroups in it. Subgroups make use of ATP to pump a large number of substrates carrying charge across various biological membranes and are differentiated on the basis of phosphorylated intermediate during the reaction process. Based on the type of substrate, P-type ATPase transport, they are sorted into five groups.

CPx ATPases belong to P-type ATPases, which have been associated with heavy metal transportation across the cell membrane (Solioz and Vulpe 1996). CPx ATPases are not only responsible for the absorption of heavy metal in the plants but also prevent the accumulation of heavy metals to deleterious extent. In human Menkes disorder, the gene encodes a defected copper pump, which results in the accumulation of copper to toxic levels. CPx ATPases are generally linked with Cu and Cd translocation; nevertheless, in *E. coli* and *Synechocystis* PCC 6803, they have been linked with Zn translocation too (Beard et al. 1997).

Copper (Cu) is a metal that holds a unique position, as far as its role in plants is considered. It is both a blessing and a menace for a cell, and the only thing that matters is its amount. Therefore, to maintain such a delicate balance, several constituents play their part. P-type ATPase copper transporters, which are homologous to human and yeast genes, have been reported to regulate the transport of copper across the endomembrane system in Arabidopsis (Hirayama et al. 1999; Woeste and Kieber 2000). Burkhead et al. (2009) stated that heavy metal transferring P-type ATPases (HMAs) five to eight are found to be related to Cu homeostasis. Nevertheless, HMA 5 among all four of them has been greatly linked with outflow of Cu and vascular translocation. It has been found in inordinate amounts in both plant roots and flowers and are significantly increased, when plethora of Cu gets accumulated in these plant parts (Andrés-Colás et al. 2006).

According to Axelsen and Palmgren (2001), three other putative Cu-translocating genes have been recognized; however, their mode of action has not been eloquently described. Cu transfer to chloroplast is also vital as it serves as a cofactor for stromal enzyme copper/zinc superoxide dismutase (Cu/Zn SOD) and for thylakoid lumen protein, which plays role in ETC initiating in cytochrome B_6f complex and culminating in photosystem I. In this transfer of Cu to chloroplast, the role of P-type ATPase Cu transporter cannot be discounted (Shikanai et al. 2003).

13.4 COPT Copper Transporters

The dual nature of Cu has led the plants and other organisms to develop an advanced homeostatic network in order to control uptake, transfer, utilization, and detoxification/export of Cu (Himelblau and Amasino 2000; Clemens 2001). The Cu homeostasis involves a main step regarding the uptake of Cu via cell membrane, and for mediation of its uptake, different forms of transporter proteins have been reported. Among these, the main group is the COPT (COPper transporter)/Ctr (Copper transporter) proteins belonging to several protein families in diverse organisms (Puig and Thiele 2002). Another transporter type for Cu movement from cytosol into organelles in plants and humans is P-type adenosine triphosphate pump (Williams et al. 2000; Williams and Mills 2005). In few studies, it has also been documented that other metal transporters can also carry Cu into the cells. For example, in Arabidopsis, two transporters of OPT/YSL Fe transporter family, namely, YSL1 and YSL3, can carry Cu from plant leaves to seeds (Waters et al.

2006). Similarly, ZIP2 and ZIP4 belonging to ZIP Zn transporter family transport Cu (Puig et al. 2007a, b).

The role of COPT/Ctr proteins in Cu uptake has been described principally in yeast, *Saccharomyces cerevisiae* (Dancis et al. 1994). Later, COPT/Ctr proteins transporting Cu were characterized in diverse organisms, for instance, in the case of plants: AtCOPT1, AtCOPT2, AtCOPT3, AtCOPT4, and AtCOPT5 in Arabidopsis (Sancenon et al. 2004) and OsCOPT1 and OsCOPT5 in rice (Yuan et al. 2010). In rice, the COPT family is composed of seven members, COPT1 to COPT7. Among these, COPT1 and COPT5 are able to develop homodimers or a heterodimer. Both of these COPTs can bind to multiple sites of XA13 protein in rice, which is considered as a susceptible protein to plant pathogenic bacterium *Xanthomonas oryzae* pv. *oryzae* (Xoo) (Yuan et al. 2010). Except the two COPTs, namely, COPT1 and COPT5, the rest of COPTs have been described to function individually or jointly to carry Cu transport in distinctive rice tissues (Yuan et al. 2011).

Copper ($Cu^{+}2$) gets reduced to Cu+, in order to be carried by COPT transporters. The COPT family comprises of six constituents, among which COPT1, COPT2, and COPT6 exist on plasma membrane and COPT3 and COPT5 in internal membranes. Cu uptake by COPT proteins is an important phenomenon and has been studied by comparable yeast mutants (Sanz et al. 2019). Seven member COPT-type gene families are found in rice plant, one of the major crop plants found in the world (Yuan et al. 2011). COPT proteins have been reported in transfer of Cu in many major parts of plants. Puig (2014) reviewed and stated that COPT1 plays role in absorption of Cu in plant roots, COPT6 plays role in the distribution of Cu in plant shoots, and COPT5 activates and organizes Cu from organelles meant for storage. Therefore, in the light of aforementioned functions of COPT proteins, it can be stated that the COPT proteins play an indispensable role in Cu homeostasis in plant. COPT regulates Cu, which has a role in Arabidopsis circadian clock. Sancenon et al. (2004) reported that during the period of Cu shortage, COPT1 in SPL7-dependent fashion gets activated, which ensures efficient absorption of Cu from a culture medium. Perea-García et al. (2013) reported, that in response to Cu scarcity, expression enhances manifold in SPL7-dependent manner. Furthermore, the expression of two transport proteins of ZIP family, ZIP2 and ZIP4, that mediate the transport of divalent cations is regulated by the presence of Cu (Wintz et al. 2003; Del Pozo et al. 2010).

13.5 Copper Chaperones

Copper chaperone found in plants is similar to the one found in all eukaryotic organisms, which has been revealed by complementation studies conducted in *S. cerevisiae* (Koch et al. 1997; Peña et al. 1999). These are proteins that do not possess Cu but perform job similar to the proteins containing Cu (Andrés-Colás et al. 2006). It is vital to maintain the levels of Cu within plant cells. These are actually a set of soluble proteins, which possess a special domain that is meant to bind

Cu. Thus, their Cu-chelating potential helps them to both efficiently and effectively regulate Cu homeostasis within plant cell (Shin et al. 2012) to evade copper-induced harmful effects. Moreover, Cu chaperones carry out delivery of Cu to particular Cu proteins and compartments. Brewer (2010) highlighted the significance of maintaining Cu within plant cells, and if the levels of free Cu go unchecked, it generated super oxide and hydrogen peroxide reactive oxygen species, and hydroxyl radicals negatively affect proteins, lipids, and DNA of the cells. In order to avoid the levels of free Cu within a cell, it needs to be chelated within it. This guarantees efficient and effective transfer and homeostasis.

In the case of Arabidopsis, its genome encodes seven Cu chaperones, namely, Cu chaperone for superoxide dismutase (CCS), antioxidant protein1 (ATX1), ATX1-like Cu chaperone (CCH), cytochrome c oxidase 11 (COX11), COX17, and two homologs of the yeast Cu chaperone (HCC1 and HCC2) (Puig et al. 2007a, b; Burkhead et al. 2009; Attallah et al. 2011). CCS carries Cu to Cu/Zn superoxide dismutases (SODs) in the chloroplast, cytoplasm, and peroxisome (Burkhead et al. 2009). ATX1 and CCH exhibit maximum sequential homology with the yeast protein (ATX1), and both of these can complement the yeast ATX1 mutant; however, they possess diverse properties and roles in Cu homeostasis (Shin et al. 2012). ATX1 enhances tolerance against Cu excess as well as deficiency through its Cu-binding MXCXXC motif (Shin and Yeh 2012; Shin et al. 2012. Additionally, Cu chaperones COX11, COX17, HCC1, and HCC2 function in mitochondrial respiration (Attallah et al. 2011). While extensive studies have been conducted on Cu chaperones, considerable information is still missing, specifically involving whether Cu chaperones and Cu are transported into the nucleus and induce plant defense responses.

13.6 Natural Resistance-Associated Macrophage Protein (NRAMP)

The NRAMP genes have been widely reported in organisms ranging from bacteria to yeast, including plants, mice, and human beings. This gene family has been widely found in the transport of heavy metal divalent ions across the plasma membrane (Nevo and Nelson 2006). In plants, numerous members of this gene family have also been reported, and their functions have been characterized. For example, in the case of Arabidopsis, six NRAMP proteins have been demonstrated (Mäser et al. 2001). Among these proteins, AtNRAMP1 is responsible for regulating Fe homoeostasis (Curie et al. 2000), and as a high-affinity transporter, it is involved in the uptake of Mn (Cailliatte et al. 2010). The two proteins, namely, AtNRAMP3 and AtNRAMP4, exist on the vacuolar membrane, and during the phase of seed germination, both perform mobilization of vacuolar Fe (Lanquar et al. 2005). AtNRAMP6 is directed to endomembrane compartment, which is vesicular-shaped, and this protein works as a metal transporter intracellularly with known association with Cd tolerance (Cailliatte et al. 2009).

In rice, it has been reported that three NRAMP proteins take part in Fe, Mn, and Cd uptake (Takahashi et al. 2011; Sasaki et al. 2012; Yang et al. 2014), whereas OsNrat1 participates in the uptake of Al from tip cell walls of roots into the cell, which creates Al tolerance in rice (Li et al. 2014). Likewise, in legumes, many NRAMP genes have been detected. For example, AhNRAMP1, a NRAMP gene from peanut, has been shown that it is considerably induced by Fe deficiency in leaves and roots, and this gene, when heterologously expressed in tobacco, results in accumulation of Fe in young plant leaves and Fe deprivation tolerance (Xiong et al. 2012). Additionally, gene MtNRAMP1 is specifically restricted to the plasma membrane in case of a model legume named *Medicago truncatula*, and this gene shows highest expression levels in roots and nodules, depicting its major involvement as a transporter in apoplastic uptake of Fe in rhizobia-infected cells (Tejada-Jiménez et al. 2015).

In soyabean studies, it has been revealed that the gene regulation gets affected by the shortage of N, P, K, Fe, and S. Additionally, the regulation gets affected by the buildup of Fe, Cu, Cd, and Mn. This suggests that Gm NRAMP genes play role in various different stress-related pathways and perhaps are involved in cross talk in nutrient stress pathways (Illing et al. 2012). In order to study the Gm NRAMP responses during heavy metal stresses, expression of these genes was calculated, by exposing soyabean seedlings to plethora of Fe, Cu, Cd, and Mn. In this study, only 10NRAMP gene expression was noticeable. Under excess Cu, GmNRAMP5a expression was enhanced in both leaves and roots, and expression of GmNRAMP1a was amplified in roots; however, the expression of GmNRAMP2a was diminished in both leaves and roots, respectively. Nevertheless, two NRAMP genes exhibited a unique, rather conflicting drift in soyabean leaves and roots, in response to inordinate concentration of Cu (Qin et al. 2017).

13.7 Relating the Biosynthetic and Homeostatic Roles of Cu Transport Systems

Cu serves as a cofactor, and thus, it can be contended that all the Cu transport proteins have some role in biosynthesis of different products (Burkhead et al. 2009). One of the biosynthetic functions can be viewed in the context of three ATP-driven pumps, namely, HMA6, HMA7, and HMA8. On the other hand, homeostatic function of the transport protein can be viewed in the context of regulating apposite concentrations of Cu in different compartments both locally and widely in different plants, which can be noted over a period of time. This appears to be one of the main roles played by the members of COPT family. COPT1 and COPT5 phenotypes are found where Cu concentrations are comparatively low and are evident in tissues, where transport proteins are generally expressed; however, this cannot be explained by the absence of Cu enzyme function, and this can only be explained in terms of Cu/Zn superoxide dismutase, which stops its function at once Cu shortfall happens. This decrease in the concentration of Cu/Zn superoxide dismutase follows the increase in miR398 through SPL7 (Yamasaki et al. 2007, 2009), which is among one of the four Cu-associated RNAs (Burkhead et al. 2009). Besides other functions, it was documented that Cu micro RNAs regulate the plethora of Cu in order for it to be available as cofactor where and when needed by the Cu proteins (Burkhead et al. 2009).

Cu homeostasis in plants is controlled by the SPL7 (squamosa promoter binding protein-like) transcription factor, which is active during Cu deficiency (Yamasaki et al. 2007; Bernal et al. 2012). In case of Arabidopsis, major targets of SPL7 include the genes COPT1, COPT5, and COPT6. COPT1 is engaged in encoding high-affinity Cu transporter of the roots, which is involved in primary Cu uptake (Sancenon et al. 2004). COPT6 gene has been shown to express in shoots and is found in the plasma membrane (Jung et al. 2012). Both genes are upregulated in plants during Cu deficiency so as to enhance the absorption capability at a systemic level (COPT1) and much precisely in photosynthetic plant cells (COPT6) (Sancenon et al. 2004; Jung et al. 2012). COPT5 gene is also expressed under Cu deficiency conditions, and it carries Cu efflux from the vacuole, demonstrating its role in Cu remobilization (Klaumann et al. 2011). It has been shown that Cu binds very firmly to its targets (Lippard and Berg 1994), and consequently, any competing Cu-utilizing proteins must be removed when Cu becomes deficient to permit the favored delivery of Cu to plastocyanin. This mechanism in plants regarding “copper economy” encompasses the posttranscriptional regulation of dispensable Cu enzymes by several microRNAs, which are in turn controlled by SPL7 (Yamasaki et al. 2007). The transcripts that encode the vital Cu proteins like plastocyanin are not directed for degradation by the microRNAs (Abdel-Ghany and Pilon 2008), which suggests that such proteins are important targets for deficient Cu.

13.8 Conclusion

Copper (Cu) is a vital element, and its requirement by plants as a micronutrient, as a transporter, and as a cofactor has not been elucidated thoroughly. Nonetheless, research has been conducted in the past and is still being continued on the functions of Cu in plants. As a result of these research efforts, it has been revealed that as a micronutrient, it is required by the plants in miniscule amounts; nevertheless, it is imperative for plant growth and development. In addition to it, the role of Cu as a cofactor cannot be discounted. The role of copper as Cu proteins is sine qua non for the normal functioning of plant proteins. In the light of discussion, it can be concluded that it is sine qua non for plant’s survival; however, it should always be understood that it is required by the plants in very low amounts, and if it exceeds the limit, it can prove detrimental to plant growth and development and can even threaten its very existence. Therefore, in order to maintain such a delicate balance, plant has developed an efficient as well as an effective metal transport system, in which several players play their role to regulate the concentrations of different metals like copper in them.

Copper (Cu) homeostasis in plants is mediated by SPL7 regulator, which is the functional homolog of copper response regulator (CRR1), which has some semblance with the one reported in *Chlamydomonas reinhardtii.* To maintain the levels of Cu in plants, different transport proteins play their part. The major and the most important proteins among them include P-type ATPase copper transport proteins, which regulate movement of copper across the plasma membrane. P-type ATPase is not only responsible for the uptake of Cu in plants but also prevents its inordinate accumulation that can lead to deleterious consequences. Additionally, COPT transporters exist in plants, a six-member family, in which COPT1, COPT2, and COPT6 are located on cell membrane and COPT 3 and COPT5 are located on internal membranes. These are responsible for transport of Cu to various different parts of plants. The role of Cu chaperones, one being without Cu, is similar to the one with Cu. These too play role in the regulation of Cu within plant cells. The expression of NRamp genes also gets altered during heavy metal toxicity in plants, when studied in soyabean seedlings.

Cu transport systems have a linked function in two most significant activities occurring within a cell, that is, biosynthesis and homeostasis. Biosynthetic role can be explained in terms of three ATP-driven pumps, namely, HMA6, HMA7, and HMA8. Homeostatic role can be explained in terms of regulating apposite concentration of Cu to be made available to proteins as per requirement. Nevertheless, this hypothetical statement needs to be proven in future. To sum up, more extensive research studies are suggested to enhance our understanding of Cu homeostasis within plants. Nonetheless, as yet, we can say that Cu transport is a complex phenomenon, which is overseen by an intricate machinery built within plants.

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