

Review

Cadmium Accumulation in Cereal Crops and Tobacco: A Review

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Abstract: Cadmium (Cd) is a toxic heavy metal with no known biological function in plants and one of the most toxic substances released into the environment. Crops, such as rice, maize, wheat and tobacco are the major sources of Cd for humans. Cd toxicity inhibits crop growth and development by affecting many central physiological and biochemical processes, and finally it affects human health via the food chain. To adapt to Cd toxicity, crops have evolved a series of detoxification mechanisms. Immediate responses include rapid changes at the transcriptional level with simultaneous changes at the physiological and metabolic levels. However, the long-term responses involve genetic modifications and epigenetic changes. During the last decade, many genes involved in Cd uptake and translocation have been identified, and many of them are transporters. To decrease the accumulation of Cd in cereal grains and tobacco leaves, a number of approaches have been proposed, including physical and chemical methods, developing and planting low accumulation genotypes using transgenic strategies or marker–trait association breeding. In this review, we describe the toxicity of Cd to crops and human body, advances in the molecular mechanisms of Cd accumulation in cereal crops and tobacco, and approaches to decrease Cd accumulation.

Keywords: cereal crops; tobacco; Cd accumulation; molecular mechanism; transporter; transcription factor; epigenetic regulation; alleviating approaches

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1. Introduction

With the rapid industrialization and urbanization, soil cadmium (Cd) contamination has become a serious environmental issue worldwide [1]. Although the source of soil Cd contains a contribution from natural factors such as atmospheric deposition and weathering of geological parent materials, human activities are the main contributors [2,3]. Anthropogenic activities, such as mining, the application of phosphate fertilizers and sewage sludge, the cement industry, and the production of nickel–cadmium batteries and plastics, are the major sources of Cd [4,5]. The mean value of Cd content in non-contaminated soils range from 0.06 to 1.1 mg kg^{−1} with the minimum and maximum of 0.01 and 2.7 mg kg^{−1}, respectively [6]. A survey reported by the Ministry of Environmental Protection and the Ministry of Land and Resources of the People's Republic of China showed that 7% of farmland is polluted by Cd [3]. Therefore, Cd has been identified as the most prominent hazardous pollutant in field [7]. Given the prevalence of Cd pollution, WHO has set the safety thresholds for cereal grains, which are 0.4 mg kg^{−1} for rice, 0.2 mg kg^{−1} for wheat, and 0.1 mg kg^{−1} for maize [1]. The tobacco products still lack a uniform standard like that of the cereal crops [8,9]. WHO [10] reported that smoking leads to a substantial intake of toxic metal (loid)s (Cd, Pb, Cr, Ni and As) to both smokers and non-smokers by passive smoking. Smoking tobacco from Cd-polluted fields leads to an unacceptable intake of Cd for local males (4.2 mg kg^{−1} year^{−1}) and females (4.9 mg kg^{−1} year^{−1}) [8].

Smoking may elevate the kidney Cd content of male smokers by about 16-fold at age 50 [9]. In southern China, cereal crops such as rice and tobacco rotation is a common farming practice which can effectively improve crop yield and farmer income, and inhibit disease and insects [11]. The rotation has been found to be effective in alleviating Cd pollution of rice soil as a result of the higher capacity of Cd accumulation in tobacco under lab conditions, but inconsistent results were found under field conditions [9]. Cereal crops and tobacco are two major sources of Cd intake for humans. Hence, the current review summarizes the toxic effects of Cd on crops and humans and emphasizes the main genes involved in Cd uptake, translocation and accumulation in main cereal crops and tobacco. Moreover, remediation strategies to decrease Cd accumulation are also highlighted.

2. Cd Toxicity

Cd toxicity severely inhibits crop yield and quality by affecting key physiological and biochemical processes, such as inhibition of photosynthesis, cell wall biosynthesis and remodeling, energy production and protein synthesis [12,13]. At the cellular level, Cd could have a series of interactions with intracellular substances, such as binding with sulfhydryl groups of central proteins, changing the structure of these proteins, and finally inhibiting their activity [14]. Cd toxicity severely damages cell ultrastructure with swollen mitochondrial cristae and chloroplast, reduces the number of chloroplasts and increases the number of osmiophilic plastoglobuli [15]. The Cd-induced growth inhibition is associated with programmed cell death with reduced numbers of nuclei, DNA damage and increased cell death [16]. Besides, Cd activates reactive oxygen species (ROS) over-accumulation, induces oxidative damage to many important biomolecules and membrane systems, and eventually inhibits plant growth [17,18]. The inhibition of the uptake and translocation of essential micronutrients can also contribute to Cd toxicity. Cd inhibits the uptake of Zn, Fe and Mn likely by competing for transporters or interfering with the regulation of transporter gene expression [19,20]. Cd stress also obviously inhibits nitrogen and phosphorus uptake to the grain of wheat [21]. Cd is absorbed and finally accumulated in edible parts of crops. When it exceeds a certain level, it will not only seriously affect the yield and quality of crops, but also threaten the health of humans and animals through the food chain [22]. Crops growing on fields with soil Cd content insufficient to affect growth can still over-accumulate Cd in seeds at a sufficient level to threaten human health [1]. Therefore, more attention has been paid to the threat of Cd to human health rather than to crops.

Large scale awareness of Cd toxicity in humans arose with the outbreak of “Itai-itai” disease in Toyama Prefecture, Japan which is the first known Cd poisoning in the world [23]. Once Cd enters the body, the damage caused to human and animal health is hard to recover or even pass on to the next generations. Its toxic effects on humans and animals are as follows: (1) The blood system: Cd can activate the production of ROS in the blood, causing oxidative damage to the red blood cells and decreasing the red blood cell counts, hemoglobin content and hematocrit value [24]. (2) Human and animal organs: Cd treatment induces ROS accumulation in liver and brain and significantly decreases the activity of glutathione S-transferase, alanine aminotransferase and alkaline phosphatase in liver and acetylcholinesterase in brain [25]. The toxic effects of Cd on the brain, kidney, respiratory system and reproductive system have been reported [26]. (3) The immune system: After entering the body, Cd will accumulate in the immune cells, affect the normal function of the immune system, and finally induce health problems [27]. (4) DNA repair: Cd inhibits the DNA repair system via affecting key proteins involved in DNA excision and mismatch repair, thereby increasing the risk of carcinogenesis [28,29].

3. Cadmium Uptake, Translocation and Accumulation in Cereal Crops

There are several steps for Cd to translocate from soil to grain, including root uptake, root-to-shoot translocation and distribution to grain [30]. Genotypic differences in Cd accumulation have been found in various crop species. For example, there are significant

genotypic differences in grain Cd concentration in maize and rice grown in non-Cd polluted fields [15,31]. The potential of Cd uptake has been evaluated in an attempt to explain the variations in Cd accumulation identified among different genotypes. However, Cd accumulation is much more complex than simply differences in Cd uptake.

The ability of roots to uptake Cd from the soil is affected by many factors, such as soil pH, available Cd concentration, organic matter and other chemical elements [31–34]. Xie et al. [34] investigated the effect of combined application of four different heavy metals (Cd, lead, chromium and copper) on growth and heavy metal concentration in different tissues of rice. The interactions among the four heavy metals in soil affect the concentration of seed Cd, Cr and Cu. Cd accumulation increases with the pH increases from 3.5 to 6.0, while in the range of 7.0–8.0, it decreases with the increase in the pH value in rice [32]. Grain Cd concentrations of maize are higher in low pH fields (pH 5.68–6.08) than that in high pH fields (pH 7.51–8.14) [33]. Moreover, rhizosphere microorganisms and root exudates can reduce root uptake of Cd²⁺ [35,36]. H₂S produced by some sulfur bacteria can form CdS precipitation in soil Cd, which can decrease root Cd uptake [37].

After Cd²⁺ is absorbed by roots, part of Cd²⁺ combines with phytochelate to form the non-toxic chelates. The remaining Cd²⁺ competes for transporters of other divalent metal ions and is transferred from root epidermal cells to vascular bundles to be involved in the xylem and phloem loading of Cd, and finally it is transferred from the root system to the shoot [38]. Meanwhile, crops activate the third line of defense against Cd stress, including up-regulating the expression of vascular membrane-localized transporters and accelerating the transportation of Cd²⁺ and Cd-chelates into vacuoles, and up-regulating the expression of Cd efflux transporters [33,39].

3.1. Multi-Omics Approaches Are Powerful Tools for Elucidating the Molecular Mechanisms of Cd Accumulation

In recent years, multi-omics and bioinformatic approaches, which have been widely used in various plant species, have provided a huge amount of data to investigate the molecular mechanisms of Cd transport and accumulation [40]. According to these investigations, the identified differentially expressed genes can be classified into five categories, including metabolic pathways, organic acids, transporters, phytohormones and ROS production [41]. For instance, Huang et al. [42] compared the differences between *Nicotiana tabacum* L. and *Nicotiana rustica* L. using transcriptome sequencing and found that the higher Cd accumulation in leaves of *N. tabacum* depends on comprehensive coordination of Cd transport, including less cell wall binding, weaker impediment by the Casparian strip, and higher efficient xylem loading. In barley, genes related to reactive oxygen species metabolism, cell wall formation and maintenance, ion membrane transport and stress response are identified [17].

Root absorption is the first step for grain Cd accumulation and root Cd retention plays an important function in low Cd accumulation [43]. The response of cell wall synthesis and GSH metabolism are two major mechanisms for root Cd retention in Cd-safe genotype by transcriptomic analysis [43]. Similar results are reported by Huang et al. [44]. Besides root, the nodes play a key role in grain Cd accumulation by regulating the redistribution of Cd in nodes [45–47]. Grain Cd concentration in rice shows a significantly positive correlation with upper node Cd concentration and root-to-shoot Cd translocation rate [47]. Distinct roles in Cd translocation and distribution in nodes of wheat are identified, and the uppermost node plays a key role in restricting Cd translocation to grain in wheat [48]. The results demonstrate that key genes in nodes are involved in Cd redistribution. Liu et al. [49] investigated the genotypic differences in gene and microRNA expression patterns in panicle node and first node in response to Cd using two rice genotypes differing in grain Cd accumulation. Differential expression of several genes, such as *OsNramp5*, *OsIRT1* and *OsABCC1*, lead to a different pattern of Cd accumulation in different nodes [49]. Combined analysis of transcriptome and WGCNA showed that higher expression levels of metal

transporters existed in unelongated node (Node A) near the root than that in the panicle node (Node B) [46]. Node A is a key factor for regulating Cd transfer to the panicle.

3.2. Main Transporter Families of Cd in Cereal Crops

Plant cell membrane systems contain various transporters for Cd uptake (Figure 1; Table 1). Although no specific transporters for Cd have been identified, many transporters associated with Zn, Mn and Fe have been found to be involved in Cd uptake and translocation [23,50,51]. Among these transporters, some transporter families play key roles in Cd uptake and translocation. Several members of natural resistance-associated macrophage protein (NRAMP) family have been verified to transport Cd^{2+} in various crop species. In rice, *OsNRAMP5* has been proved to be a major transporter for Cd uptake [52]. The suppression of *OsNRAMP5* significantly increases the root-to-shoot Cd translocation [52,53]. *HvNramp5* also mediates the uptake and translocation of Cd and Mn in barley. Knock-down of this gene significantly decreases Cd and Mn content in both roots and shoots of barley seedlings [54]. A higher ability of Cd uptake in rice than in wheat and maize can be explained by the fact that rice has a higher expression level of *Nramp5* [55]. Besides *OsNRAMP5*, *OsNRAMP1* is also involved in Cd and Mn uptake in rice, and its function is similar to *OsNRAMP5*, but not redundant [56].

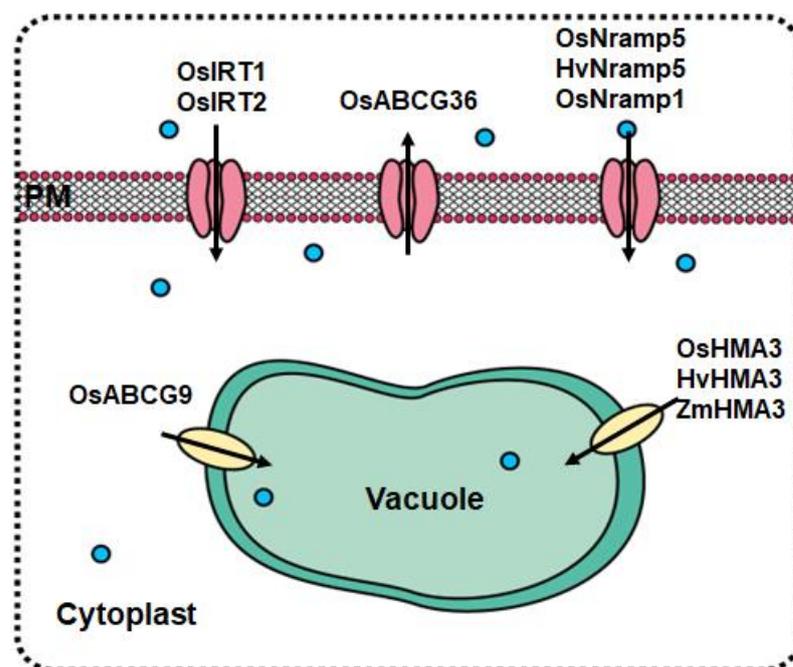


Figure 1. Schematic diagram of main Cd transporters involved in Cd uptake, efflux and vacuolar sequestration in root. PM, plasma membrane.

Heavy metal associated transporters (HMAs) are P-type ATPases that usually act as efflux pumps, removing unwanted ions from cells. Among these members of the HMA family, HMA3 plays a major function in grain Cd accumulation in various crop species [33,39]. For instance, overexpression of *OsHMA3* significantly improves the Cd tolerance via sequestering Cd into vacuoles thus decreasing the grain Cd content in rice [39]. Tang et al. [33] performed a large-scale genome-wide association analysis of grain Cd concentration in maize and found *ZmHMA3* is the major gene for low grain Cd accumulation. Similar results are also found in barley [57]. Insertion of a 3.3 kb Sukkula-like transposable element in upstream of *HvHMA3* elevates the expression of this gene and the introgression of the insertion to commercial barley cultivar significantly decreases grain Cd content without yield penalty [57]. In addition, *OsHMA2* has also been identified to

involve in root-to-shoot translocation of Cd and Cd transport to seeds. Overexpression of *OsHMA2* in rice shows lower grain Cd content than wild types [58].

ATP-binding cassette (ABC) transporter family is widely involved in the transport of heavy metals, metalloids, ions and lipids in plants [59]. However, few ABC transporters are found to be involved in Cd uptake or transport in cereal crops, and most of these genes are characterized in rice [60–62]. *OsABCG36* is localized in roots and knockout of this gene induces elevated Cd content in root cell sap [60]. A further study found that *OsABCG36* is involved in exporting Cd from root cells, but it does not participate in shoot Cd accumulation [60]. *OsABCG48* and a tonoplast-localized C-type ABC transporter *OsABCC9* are involved in Cd tolerance and accumulation in rice [61,62].

In addition, several transporters, *OsCd1*, *OsLCT1*, *OsLCD*, *OsCCX2*, *OsZIP1*, *OsIRT1* and *OsIRT2*, are all involved in Cd uptake, transport or accumulation in rice (Figure 1), [45,63–67]. Natural variation of *OsCd1* plays key roles in the divergence of grain Cd accumulation between rice subspecies [67]. The nodes in rice are critically involved in xylem to phloem Cd transport and, thus, are responsible for grain Cd accumulation. *OsLCT1* is detected in the uppermost node and strongly expressed during reproductive stage [45,65]. Knockout of this gene significantly decreases phloem-mediated Cd transport, but did not affect xylem-mediated transport. Another node-expressed transporter, *OsCCX2*, also mediates grain Cd accumulation in rice [64].

3.3. Transcription Factors Associated with Cd Transport and Epigenetic Regulation in Cereal Crops

Cd-induced regulation of gene expression is mediated by changes in the activity of transcription factors (TFs). Many TF families, such as WRKY, bZIP, MYB, ERF and HSF, have been identified to be affected by Cd stress. After 12 d Cd treatment, most of the Cd-induced miRNA-target genes are transcription factors in rice by combined analysis of transcriptome, miRNA sequencing and degradome, such as *ARF13*, *SPLs* and *NACs* [68]. One hundred and ninety-eight genes encoding MYB repeats are identified in Arabidopsis and rice, respectively [69]. Among them, about 20% of these genes responses to Cd stress. For instance, overexpression of the Cd-induced MYB49 gene in Arabidopsis results in a significant increase in Cd accumulation, whereas *myb49* knockout plants reduce the accumulation of Cd [70]. In addition, knock-down of *OsMYB45* inhibits plant growth by increasing ROS accumulation and decreasing antioxidant enzyme activity [71]. Heat shock transcription factors play an important function in various abiotic and biotic stress, such as Cd toxicity [72]. For instance, wheat and rice *heat shock transcription factor A4a* is involved in Cd tolerance through upregulating the expression of metallothionein [72]. *TaWRKY70* directly binds to the promoter of *TaCAT5* and regulates Cd tolerance through accumulating Cd in roots but not in the leaves of transgenic Arabidopsis [73]. *ZmWRKY4* confers Cd tolerance by elevating the activity of superoxide dismutase and ascorbate peroxidase [74]. Ethylene responsive transcription factor (ERF) family is widely involved in various biological processes including stress response. Durum wheat has been reported to accumulate more Cd than other cereal crops [75]. Djemal and Khoudi [76] identified an ERF from durum wheat (*TdSHN1*) that confers Cd tolerance in transgenic plants. The transgenic tobacco plants show high SOD and POD activity and low ROS production compared with wild types. The NAC transcription factor family plays crucial roles in plant growth, development and stress tolerance. *OsNAC300* is mainly expressed in roots and highly upregulated by Cd treatment [77]. Overexpression of *OsNAC300* obviously improves Cd tolerance by activating the transcription of *OsPR10a*, *OsPR10b*, and *OsCHS1* in rice. Heterologous expression of *AemNAC2* and *AemNAC3* in wheat significantly decreases grain Cd concentration [78].

Epigenetic regulation in plants contains DNA, histone and RNA modification which can modulate gene expression in response to environmental stimuli [79]. DNA methylation is an important type of DNA modification that plays a key role in gene regulation, DNA replication and repair, and chromatin determination [80]. Sun et al. [81] investigated the effects of cadmium exposure on soybean genomic DNA methylation levels and patterns

and revealed that soybean resists Cd stress by increasing both the level of genomic DNA methylation and the genomic DNA remethylating rate. Shafiq et al. [82] investigated the effect of Cd stress on the DNA methylation levels in two wheat genotypes and how it affects metal tolerance. Results showed that the expression of *TaHMA2* and *TaABCC2/3/4* are significantly upregulated in Cd tolerant genotypes compared with Cd sensitive genotypes under Cd treatment. A further study demonstrates that genes mediating DNA demethylation are inhibited by Cd and, in turn, enhance plant tolerance to Cd stress by improving Fe nutrition through a feedback mechanism [83]. An m⁶A methylation analysis is performed to identify Cd responding-related modified m⁶A sites in barley [84]. More than 8000 sites and 3900 differentially expressed genes are found. Interestingly, no m⁶A methylation sites are found in the main transporters involved in Cd uptake and translocation in barley, but modified sites are identified in several transcription factor family members, such as MYB and WRKY [84]. The association between m⁶A modification and Cd tolerance is built after the finding of coordination of m⁶A methylation and gene transcriptome in rice [85]. Unlike Arabidopsis, the m⁶A-modified nucleotide in rice shows a preference to the stop codon and 3' UTRs [85].

In plants, non-coding RNAs are known as epigenetic modulators. It regulates gene expression against Cd stress at the post-transcriptional level [86,87]. miRNA390, which is conserved in maize, rice, and Arabidopsis, plays vital roles in abiotic stress response. Transgenic rice plants overexpressing miR390 displays reduced Cd tolerance and higher Cd accumulation compared with wild-type plants [87]. miRNA166 is verified to be involved in Cd accumulation [86]. Overexpression of miRNA166 significantly decreases root-to-shoot Cd translocation and grain Cd accumulation. Zhou et al. [88] identified the regulatory mechanisms between heavy metal ATPases (HMAs) and microRNAs in *Triticum aestivum* L. under Cd stress. In conclusion, the interplay among different types of epigenetic regulation provides plants with a multilayered and robust epigenetic mechanism to improve survival under Cd stress.

4. Key Genes Involved in Cd Accumulation and Tolerance in Tobacco

Besides cereal crops, tobacco is also a major source of Cd intake for humans. The key genes associated with Cd accumulation and tolerance in tobacco are listed in Table 2. Three homologous genes of HMA4, Nramp5 and Nramp1 have been characterized to be involved in Cd uptake and transport in tobacco [89–91]. *NtNramp5*, a homolog of *OsNramp5*, is a transporter for Cd and a mutation in the coding region of this gene may explain the genotypic difference in Cd accumulation in tobacco [89]. Compared with wildtype, overexpression of *NtNramp1* significantly increases Cd concentration in roots and reduces Cd content in shoots [91]. *NtNramp3* is localized to the tonoplast and knock-out of *NtNramp3* elevates Cd tolerance through decreasing vacuole-to-cytoplasm Cd transfer [92]. Overexpression of tobacco *thioredoxin-like protein CDSP32* ameliorates Cd-induced photoinhibition by promoting the synthesis of chlorophyll and stabilizing the electron transfer chain [93]. Liedschulte et al. [90] investigated the function of *NtHMA4* in Cd accumulation and found that knockout of *NtHMA4* in tobacco reduced root-to-shoot Cd translocation by more than 90%, indicating this gene plays major roles in Cd transfer in tobacco. An iron transporter *NtPIC* also mediates Cd tolerance in tobacco [94]. Overexpressing plants show higher biomass and shoot Fe contents, longer roots, and lower Cd concentration than wildtype plants under Cd stress. However, most of these genes are all homologous genes of the identified transport genes in rice or Arabidopsis. Whether they are the main transporters involved in Cd uptake and transfer in tobacco needs to be further confirmed.

Table 1. Transporters, transcription factors and miRNAs involved in Cd accumulation in cereals.

Category	Gene Name	Materials	Cd Treatment	Subcellular Localization	Function	Reference
Transporter	<i>Oryza sativa</i> <i>OsCd1</i> ↑	Rice mutant	1 μM/0.18 mg kg ⁻¹	PM	Uptake of Cd	[67]
	<i>OsLCD</i> ↓	Rice mutant	100 μM	PM	Efflux of Cd	[95]
	<i>OsCCX2</i> ↑	Rice mutant	0.1 μM/3.9 mg kg ⁻¹	PM	Cd loading into xylem	[64]
	<i>OsZIP1</i>	Rice overexpression lines	80 μM	PM	Efflux of Zn, Cu and Cd	[66]
	<i>OsIRT1</i>	Rice overexpression lines	100 μM	PM	Uptake of Fe, Zn, Mn and Cd	[96]
	<i>OsIRT2</i>	Rice overexpression lines	20 μM	PM	Uptake of Fe, Zn, Mn and Cd	[96]
	<i>OsABCG36</i>	Rice mutant	5 mM	PM	Efflux of Cd	[60]
	<i>OsABCG48</i>	Heterologous expression in Arabidopsis	0.5 nM	PM	Efflux of Cd	[61]
	<i>OsLCT1</i> ↓	Rice RNAi lines	0.198 mg kg ⁻¹	PM	Efflux of Cd, Ca, Mg, and Mn	[45]
	<i>OsNramp1</i>	Rice mutant	0.5 μM/0.88 mg kg ⁻¹	PM	Uptake of Mn and Cd	[56]
	<i>OsNramp5</i> ↑	Rice mutant	0.5 and 2.5 μM, 1.69, 2.37 and 1.53 mg kg ⁻¹	PM	Uptake of Mn and Cd	[97]
	<i>OsHMA3</i> ↓	Rice overexpression lines	1 μM	Tonoplast	Cd sequestration in root vacuoles	[39,98]
	<i>OsHMA2</i> ↑	Rice overexpression lines	50 nM	PM	Cd loading to the xylem	[58]
	<i>Zea mays</i> <i>ZmHMA3</i> ↓	EMS mutant	2.24 mg kg ⁻¹	Tonoplast	Cd sequestration in root vacuoles	[33]
	<i>Hordeum vulgare</i> <i>HoNramp5</i>	Barley mutant	1 μM	PM	Uptake of Mn and Cd	[54]
<i>HoHMA3</i> ↓	Rice mutant	0.5 μM/0.63 mg kg ⁻¹	Tonoplast	Cd sequestration in root vacuoles	[57]	
Transcription Factor	<i>Triticum aestivum</i> <i>TaWRKY70</i>	Heterologous expression in Arabidopsis	20 μM	Nucleus	decreases Cd influx.	[73]
	<i>TdSHN1</i>	Transgenic tobacco	20 μM	Nucleus	confers Cd, Cu, and Zn tolerance in yeast and transgenic tobacco plants.	[76]
	<i>Zea mays</i> <i>ZmWRKY4</i>	Maize RNAi lines	400 μM	Nucleus	upregulates activities of antioxidant enzymes.	[74]
	<i>Aegilops markgrafii</i> <i>AemNAC2</i> ↓	Heterologous expression in wheat	1,050,100 μM	Nucleus	enhances Cd stress tolerance in wheat.	[78]
	<i>AemNAC3</i>	Heterologous expression in wheat	1,050,100 μM	Nucleus	enhances Cd stress tolerance in wheat.	[78]
Epigenetic Regulator	<i>Oryza sativa</i> miRNA390 ↓	Rice overexpression lines	100,200 μM		displays reduced Cd tolerance and higher Cd accumulation through regulation of its target gene, <i>OsSRK</i> .	[99]
	miRNA166 ↓	Rice overexpression lines	2 μM		miR166 decreases Cd accumulation and tolerance through regulation of its target gene, <i>OsHB4</i> .	[86]

“↓” or “↑” means genes have been identified that can increase or decrease Cd accumulation in grains. PM: Plasma Membrane.

Table 2. Genes involved in Cd accumulation and tolerance in tobacco.

Gene Name	Materials	Environment	Treatment	Reference
<i>NtHMA4.1</i> , <i>NtHMA4.2</i>	tobacco RNAi lines, EMS mutant	glasshouse, field trial	1 μM Cd	[90]
<i>NtNramp1</i>	heterologous expression in yeast, transgenic tobacco	glasshouse, synthetic medium	20, 50 μM Cd	[91]
<i>NtNramp3</i>	Knock-out lines	glasshouse	5, 20 and 50 μM Cd	[92]
<i>NtNramp5</i>	heterologous expression in yeast	glasshouse, synthetic medium	0.1, 5 μM Cd	[89]
<i>NtHb1</i>	transgenic tobacco	1/2 MS agar	50 μM	[100]
<i>NtUBC1</i>	KO Arabidopsis	1/2 MS agar	50 μM	[101]
<i>NtUBQ2</i>	transgenic tobacco, Arabidopsis mutant	1/2 MS agar	50 μM	[102]
<i>NtBADH</i>	transgenic tobacco	MS medium, greenhouse	0.2, 0.5 mM	[103]
<i>TrxCDS32</i>	transgenic tobacco	artificial culture chamber	100 μM	[93]

Besides Cd transporters, Ub-conjugating enzyme (UBC1), hemoglobin1 (Hb1), betaine aldehyde dehydrogenase (BADH) and Ub-extension protein (UBQ) all positively regulate Cd tolerance in tobacco (Table 2) [100–103]. Overexpression of these genes significantly enhance Cd tolerance and decrease Cd content. Meanwhile, UBC1 and UBQ2 also alleviate Cd-induced oxidative stress.

5. Approaches to Decrease Cd Accumulation

Once Cd is released into the soil, the accumulation process is irreversible, due to its long half-life and inability to be decomposed by soil microorganisms. Therefore, the most important thing to control soil Cd pollution is to control the source of Cd-contained pollutants and reduce the discharge of industrial wastewater and waste residue. For the contaminated field, agronomic approaches, bioremediation and chemical regulation can be used to restore the soil.

Physical remediation is an effective and fast strategy to solve soil Cd pollution, including soil replacement and dilution. In Japan, the surface soil of some paddy fields contaminated by Cd can always be removed and replaced [22,104]. Nonetheless, the high costs make its implementation impractical for large-scale polluted fields. Hence, soil turnover and dilution have been widely used options for lightly Cd-contaminated paddy soils [105]. The solutions mainly contain organic acids, iron salts or metal chelators. For example, Ren et al. [106] developed a novel magnetic EDTA-modified chitosan/SiO₂/Fe₃O₄ adsorbent (EDCMS) for the removal of Cd from an aqueous solution. FeCl₃ solution can also effectively remove soil Cd by regulating pH value [107]. The Cd accumulation in crops is not only affected by soil Cd level but also influenced by agronomic measures, such as water and fertilizer management [108]. For instance, intermittent irrigation with three-day flooding and five-day drainage is found to effectively decrease the accumulation of As and Cd in rice grain [109]. Different forms of N fertilizer affect grain Cd accumulation in rice [110]. Compared with the application of NH₄⁺-N, NO₃⁺-N-treated rice plants accumulated higher Cd in grain. NH₄⁺ competes with Cd for the binding sites in roots and decreases Cd uptake [111]. Therefore, the application of fertilizers rich in Cd or promoting Cd absorption should be avoided or reduced. Though physical remediation and agronomic strategies can effectively lower soil Cd pollution, growing high-Cd-accumulating cultivars may still lead to Cd concentration in edible parts of crops exceeding the thresholds, even in non-polluted fields [112]. For this reason, screening and cultivating low grain-Cd-accumulating cultivars is another effective method to cope with slightly polluted soil. Lin et al. [15] grew 95 inbred lines in the field and identified low-grain-Cd accumulation genotypes in maize. Similar results are also found in rice, barley and wheat [113–116].

Bioremediation which contains plant, animal and microorganism repair is another method to reduce Cd content in the soil. The technologies of phytoremediation include phytoextraction, phytofiltration, phytostabilization, phytovolatilization, and phytodegradation [117]. To be specific, hyperaccumulators should possess high Cd tolerance and high root-to-shoot translocation [118]. For example, *Noccaea caerulea* which has a specific capacity for Cd and Zn, is an extremophile heavy metal hyperaccumulator and has a potential for effective phytoextraction of Cd from Cd-contaminated soil [119–121]. Rhizosphere microbes have a greater ability to secrete organic acid to chelate Cd²⁺, which contributes to Cd resistance [35]. For instance, Cd stress can directly or indirectly activate Cd-related bacteria to increase the diversity of bacteria and change their colony structure in soil [122]. In wheat, two genotypes with differences in Cd accumulation have different rhizosphere microbial metabolic activities. Under Cd stress, low-accumulating wheat genotype accumulates a large number of urease-producing and heavy metal-resistant bacteria, which could increase the soil pH value and improve Cd resistance [123].

The chemical strategy is to reduce the uptake and transport of Cd by foliar spraying or direct addition to the soil based on the principle that certain chemical agents can chelate or compete with Cd in crops. Si and Se have a synergistic effect on the amelioration of Cd toxicity mainly via regulating gene expression, sequestering Cd into the root cell walls and

organelles, and reducing Cd transfer to the shoots [124]. Silicon-rich biochar or Si-fertilizer has a broad prospect to decrease Cd translocation and uptake [125,126]. Besides Si and Se, the application of other chemicals or hormone has been found to effectively reduce Cd accumulation [127–129].

There are several steps for Cd from soil to grain and many transporters involve in these processes. Therefore, the use of transgenic technologies to breed low grain-Cd-accumulating cultivars is also considered to be an effective method to reduce the absorption of Cd by crops. The key to transgenic technology is that the target genes can be efficiently expressed in plants and have the corresponding genetic and biological characteristics without changing the yield and quality of crops. For example, knockout of OsNramp5 using the CRISPR/Cas9 system can be used to produce low Cd-accumulating rice without yield penalty [65].

6. Conclusions and Perspectives

Cd is a highly toxic and non-essential element for crops. The molecular mechanisms of grain Cd accumulation have been widely investigated during the last twenty years. Many transporters involved in Cd uptake, translocation and distribution have been identified. However, the function of these transporters is mainly verified in rice or Arabidopsis, and little is known in other crops, such as wheat, maize and tobacco. At present, the expression patterns and transcriptional regulatory mechanisms of the Cd transporters, how crops sense the signals of Cd stress, and the molecular mechanisms of vacuolar and cell wall compartmentalization of Cd in crops are still largely unknown. Therefore, further in-depth research is needed to elucidate the comprehensive regulatory mechanism of Cd accumulation in cereal crops and tobacco.

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