

Review

Plant Transcription Factors: Molecular Mechanisms in Cadmium (Cd) Detoxification and Applications for Reducing Cd Accumulation in Rice Grains

Zebin Cai, Xinxin Xu, Yao Cao, Qingxian Mo and Jicai Yi *

College of Life Sciences, South China Agricultural University, Guangzhou 510642, China; 15207611626@163.com (Z.C.); 18579210455@163.com (X.X.); 17373484489@163.com (Y.C.); 13062211316@163.com (Q.M.)

* Correspondence: jicai@scau.edu.cn; Tel.: +86-20-85282180

Abstract

Cadmium (Cd) toxicity threatens global food security and agricultural sustainability. Transcription factors (TFs) act as master regulators of the complex molecular networks involved in Cd detoxification. This review provides a focused synthesis of the molecular mechanisms governing Cd tolerance in plants, encompassing antioxidant defense, Cd chelation and sequestration, Cd uptake and transport, signal transduction, and damage repair pathways. We highlight the pivotal roles of key TFs in these specific processes, such as OsMYB45 in antioxidant defense, OsIRO2 in regulating chelation and storage, OsNAC5 in modulating Cd transport, and OsE2F in facilitating the repair of DNA and protein damage. Furthermore, we evaluate the potential of harnessing these TF-mediated regulatory mechanisms for developing low-Cd rice varieties. By delineating precise correlations between specific TFs and detoxification pathways, this review proposes actionable molecular strategies to mitigate Cd contamination, thereby contributing to ecological and food safety.

Keywords: rice (*Oryza sativa*); cadmium (Cd); abiotic stress; transcription factors (TFs)

1. Introduction

Cadmium (Cd), recognized as one of the ‘five toxic elements’, is extensively disseminated through industrial emissions, mining activities, and fertilizer application [1]. Global soil Cd contamination is intensifying due to increasing anthropogenic activities. Using an Extreme Random Tree (ERT) machine learning model that incorporates climatic, geological, pedological, topographical, and socioeconomic variables (e.g., mining intensity, irrigation ratio), Hou et al. predicted that approximately 9% of global topsoil Cd concentrations exceed national agricultural thresholds (ATs) and human health/ecological thresholds (HHETs), with hotspots concentrated in East and South Asia [2]. China’s National Soil Pollution Survey Bulletin reports a 7.0% Cd exceedance rate in arable land, particularly severe in major rice-producing regions such as the Yangtze River Delta. As a major global cereal crop, rice (*Oryza sativa* L.) is a primary caloric source for billions of people. Its significance is particularly pronounced in Southeast Asia, where it is a dietary staple. Compared to other cereals like wheat or maize, rice exhibits a higher propensity for Cd uptake, resulting in pronounced Cd accumulation in grains [3]. Global

Academic Editor: Ainong Shi

Received: 13 January 2026

Revised: 31 January 2026

Accepted: 3 February 2026

Published: 4 February 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\) license](https://creativecommons.org/licenses/by/4.0/).

surveys indicate that median rice grain Cd concentrations in India (27.55 µg/kg) exceed the global median (19 µg/kg), while China shows the highest median (69.3 µg/kg) [4]. In China, 2.2–10% of rice samples exceeded the national safety limit (200 µg/kg) between 2009 and 2018. Moreover, the average monthly dietary Cd intake doubled from 1990 to 2015, reaching 15.3 µg/kg body weight (bw). This intake level surpasses the safety limits set by the Agency for Toxic Substances and Disease Registry (ATSDR, 3 µg/kg bw) and the European Food Safety Authority (EFSA, 10.8 µg/kg bw) [5].

Cd enters the human body via the food chain, accumulating over time and potentially causing severe diseases such as renal dysfunction, osteomalacia, neurodegenerative disorders, and cancer [6]. ‘Itai-Itai’ disease, first documented in Japan, resulted from consuming rice irrigated with Cd-contaminated water from the Jinzū River, manifesting as hepatic fibrosis, chronic nephropathy, bronchopneumonia, and gastrointestinal disturbances [7]. In rice, Cd stress significantly inhibits root growth, reduces lateral root formation, and triggers excessive reactive oxygen species (ROS) production, leading to oxidative stress, cellular damage, organelle disruption (e.g., chloroplasts), and impaired photosynthesis, ultimately reducing biomass and grain yield [8]. Cd also competes with essential metals (e.g., Zn, Fe) for transport proteins, inhibiting nutrient uptake, exacerbating growth inhibition, and compromising grain quality [9]. For instance, Li et al. demonstrated that Cd disrupts Ca²⁺ and K⁺ uptake/translocation, significantly reducing their content in roots and shoots, contributing to chlorosis and growth inhibition [10]. Furthermore, Xie et al. reported that Cd stress reduced yields by 17–27% in the low-grain-Cd genotype Xiushui 817 and by 20–21% in the high-grain-Cd genotype Zheda 821 [11].

To counteract Cd toxicity, plants have evolved multifaceted detoxification strategies. These include activating antioxidant systems to mitigate ROS bursts; synthesizing ligands such as phytochelatins (PCs) or metallothioneins (MTs) to chelate Cd²⁺; sequestering Cd into vacuoles via tonoplast transporters; and modulating plasma membrane transporter activity to reduce uptake or enhance efflux [12] (Figure 1). These physiological processes are primarily executed by specific functional genes. For example, ABC1/2 transporters are crucial for the vacuolar sequestration of Cd-chelates [13], while *TaNCCL2-A* (encoding a sodium/calcium exchanger-like protein) alleviates Cd toxicity by increasing calcium accumulation and enhancing enzymatic antioxidant activities [14]. The spatiotemporal expression of these functional genes is precisely orchestrated by a hierarchical regulatory network of transcription factors (TFs). Prominent TF families, such as WRKY, MYB, NAC, and bHLH, act as key regulators within this network. Typically, WRKY and MYB TFs are central to modulating antioxidant defense and metal uptake, whereas NAC and bHLH TFs are indispensable for directing phytochelatin synthesis and sequestration [12,15]. Key regulators such as OsNAC5 [16], AtMYB49 [17], and OsMYB45 [18] exemplify how TFs bridge initial stress perception with downstream physiological adaptations required to maintain cellular homeostasis [19].

Moving beyond traditional family-based classifications, this review uniquely provides a systems-level framework that integrates early Cd perception with terminal grain allocation. We incorporate the latest research—encompassing epigenetic regulatory hierarchies, microRNA-encoded peptides (miPEPs), and single-cell transcriptomics—into a cohesive model of the plant Cd-response network. Unlike prior work, this synthesis reorganizes transcription factors (TFs) according to the specific detoxification mechanisms they orchestrate, such as antioxidant defense, chelation, compartmentalization, and transport regulation, thereby enhancing the mechanistic clarity of the regulatory landscape. Furthermore, we emphasize the dual functionality of certain TFs that concurrently influence Cd allocation while regulating detoxification. For example, the soybean TF GmWRKY172 [20] significantly enhances Cd tolerance and yield while reducing seed Cd accumulation. By distinguishing between “direct effector engineering”

and “systemic network reprogramming,” and by analyzing the molecular basis of genotypic variations and tissue-specific “barrier” effects, this review culminates in a forward-looking roadmap centered on three technological pillars—multi-omics integration, epigenetic decoding, and precision promoter engineering—to provide a robust foundation for the precision breeding of “Cd-safe” rice varieties.

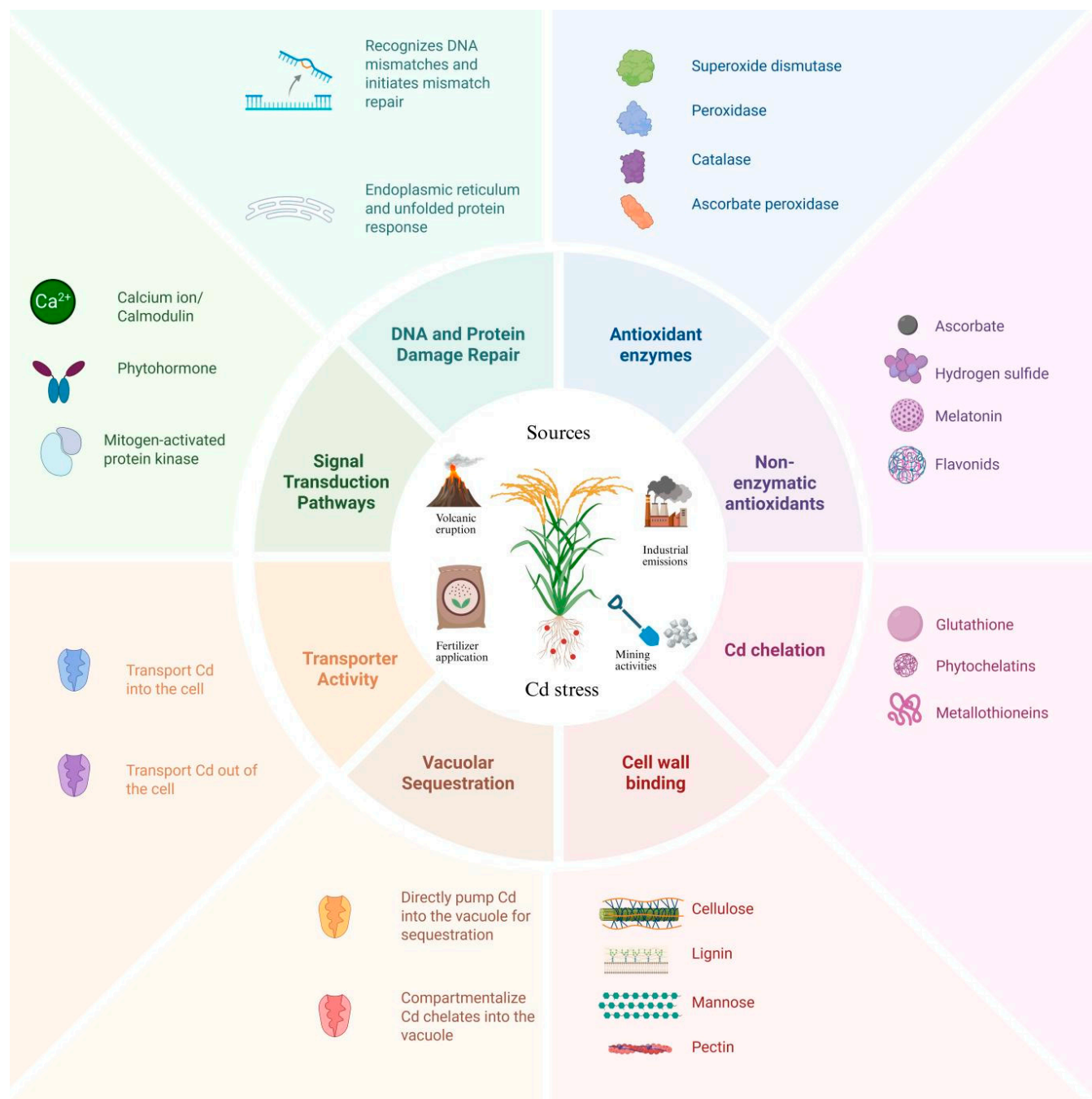


Figure 1. The sources of cadmium (Cd) contamination and Cd detoxification strategies evolved in plants during evolution. The inner circle highlights the sources of soil Cd contamination and the outer circle the strategies of transcription factor-mediated Cd tolerance regulation reviewed in Section 2. Image created in Biorender. Shiz Aoki. (2018) <https://BioRender.com/cwlzgwtd>.

2. Mechanisms and Transcription Factors Regulating Cd Tolerance and/or Accumulation in Plants

2.1. Activation of the Antioxidant Defense System

Under normal conditions, plant cells maintain ROS homeostasis through efficient antioxidant systems. Abiotic stresses such as Cd exposure disrupt this balance, triggering excessive ROS production. Elevated ROS levels cause damage to DNA and proteins, impair photosynthesis and respiration, and may induce programmed cell death. Plants employ multi-layered antioxidant defenses comprising enzymatic and non-enzymatic components. Under Cd stress, ROS also act as signaling molecules that activate stress-responsive TFs, which enhance enzymatic ROS scavenging or stimulate non-enzymatic antioxidant synthesis, maintaining cellular redox homeostasis [21].

2.1.1. Enzymatic Antioxidant System

The enzymatic antioxidant system includes peroxidase (POD), superoxide dismutase (SOD), ascorbate peroxidase (APX), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPX), which collectively mitigate ROS via precise catalytic reactions [22]. Cd-tolerant species typically exhibit higher activities of SOD, POD, and APX, whereas Cd-sensitive plants show reduced expression of antioxidant enzyme genes [23].

Studies demonstrate that Cd stress activates TFs that regulate antioxidant enzyme expression, alleviating oxidative damage (Table 1). In *Populus*, PyWRKY75 overexpression enhances POD, SOD, CAT, and APX activities, increasing Cd tolerance and accumulation [24]. In *Tamarix hispida*, ThRAX2 upregulates SOD activity and transporter function, improving ion homeostasis and Cd tolerance while reducing Cd accumulation [25]. Conversely, ThDIV2 overexpression elevates ROS and proline levels by suppressing SOD, POD, and CAT activities, negatively regulating Cd tolerance [26]. ThbZIP1 overexpression enhances POD/SOD activities and soluble protein/sugar content, bolstering Cd tolerance [27]. In soybean, Cd-induced GmWRKY172 reduces malondialdehyde (MDA) and H₂O₂ levels while increasing flavonoids, lignin, and POD activity, enhancing tolerance and reducing shoot Cd accumulation [20].

In crops, TFs also mitigate Cd toxicity via antioxidant regulation. In maize, Cd stress induces ZmWRKY4, which activates ABA-dependent SOD/APX expression to counteract ROS bursts [28]. Heterologous expression of wheat TaWRKY70 in *Arabidopsis* elevates CAT activity and Cd resistance [29]. The ethylene-responsive TF TdSHN1 from durum wheat confers Cd/Cu/Zn tolerance in tobacco by enhancing SOD/CAT activities, reducing ROS accumulation, and improving chlorophyll content and biomass [30]. In rice, OsMYB45 knockout doubles H₂O₂ levels and halves CAT activity, impairing Cd tolerance; complementation restores wild-type phenotypes, confirming its role in regulating CAT-mediated detoxification [18]. Heterologous expression of OsTAZ4 in *Arabidopsis* improves heavy metal resistance by suppressing ROS accumulation [31].

Table 1. Transcription factors regulating the expression of antioxidant enzyme genes.

Family	Plant	Heavy Metal (Primarily Cd)	Gene Name	Gene Function	Expression Site	Response to Cd (Inhibition/Induction)	Up/Downstream Genes	Role in Cd Tolerance	Role in Cd Accumulation	Reference
WRKY	Poplar	Cd	<i>PyWRKY75</i>	Increased chlorophyll and carotenoid content; enhanced activities of POD, SOD, CAT, and APX	/	Induced	/	Enhanced	Enhanced	[24]
WRKY	Maize	Cd	<i>ZmWRKY4</i>	Binds promoters of <i>ZmSOD4</i> and <i>ZmcAPX</i> to increase antioxidant enzyme activities	Leaf	Induced	<i>ZmSOD4</i> , <i>ZmCAX3A</i>	Enhanced	/	[28]
WRKY	Soybean	Cd	<i>GmWRKY172</i>	Increased POD activity, flavonoid, and lignin content	Leaf, flower, root, stem	Induced	/	Enhanced	Reduced	[20]
WRKY	Sorghum	Cd	<i>SbWRKY54</i>	Enhanced SOD, POD, and CAT activities; restricted Cd transport	Root, stem	Induced	<i>SbHKT2b</i>	Enhanced	Reduced	[32]
MYB	Tamarix	Cd	<i>ThRAX2</i>	Regulates intracellular ion homeostasis, transporter activity, and enhances antioxidant enzyme activities	Root, leaf	Induced (root), Inhibited (leaf)	<i>ThSOS1</i> , <i>ThCKX3</i> , <i>ThCAX3A</i> , <i>ThMYB78</i>	Enhanced	Reduced	[25]
MYB	Tamarix	Cd	<i>ThDIV2</i>	Decreased AOC, SOD, POD, CAT activities and GSH content	Root, leaf	Inhibited	<i>ThAO1</i> , <i>ThAO2</i>	Reduced	/	[26]
MYB	Rice	Cd	<i>OsMYB45</i>	Knockdown decreased expression of OsCATA and OsCATC, and reduced CAT activity	Leaf, hull, stamen, pistil, lateral root	Induced (root), Unchanged (leaf)	/	Enhanced	/	[18]
MYB	Populus euphratica	Cd	<i>PeRAX2</i>	Increased H ₂ O ₂ synthesis, inhibited CAT, SOD, POD activities, promoted Cd accumulation	Root, leaf	Induced	<i>AtANN1</i>	Reduced	Enhanced	[33]
ERF	Wheat	Cd, Cu, Zn	<i>TdSHN1</i>	Increased chlorophyll content, SOD, and CAT activities	/	Induced	/	Enhanced	/	[30]
bZIP	Tamarix	Cd	<i>ThbZIP1</i>	Enhanced POD and SOD activities, increased soluble sugar and soluble protein content	Root, leaf, stem	Induced	/	Enhanced	/	[27]
TEAD	Rice	Cd, Cr	<i>OsTAZ4</i>	Regulates ROS homeostasis; interacts with OsMYB34 and OsFHA9 to promote resistance to heavy metals	Whole plant	Induced	<i>OsMYB34</i> , <i>OsFHA9</i>	Enhanced	/	[31]

2.1.2. Non-Enzymatic Antioxidants

Non-enzymatic antioxidants (e.g., ascorbate (AsA), glutathione (GSH), hydrogen sulfide (H₂S), melatonin, flavonoids) operate synergistically with enzymatic systems across cellular compartments via electron donation, radical quenching, and redox buffering [21]. TFs critically regulate genes involved in their biosynthesis and recycling pathways (Table 2).

The AsA-GSH cycle is a key antioxidant mechanism. In *Populus*, overexpression of *SpHsfA4c* activates this pathway, elevating AsA and GSH levels and optimizing GSH/GSSG ratio to enhance Cd tolerance [34]. H₂S also significantly contributes to Cd tolerance by maintaining redox homeostasis. Notably, exogenous H₂S has been shown to upregulate both non-enzymatic AsA/GSH levels and enzymatic SOD/CAT activities, thereby ameliorating Cd toxicity in rice [35,36]. At the transcriptional level, WRKY TFs (e.g., WRKY18/40/60) regulate H₂S biosynthesis genes by binding to W-box elements in their promoters, thereby modulating endogenous H₂S production and Cd resistance [37].

Melatonin further enhances heavy metal tolerance by improving antioxidant defenses, inducing metal transporters, and stimulating GSH/PC synthesis [21,38,39]. For example, tomato heat shock factor HsfA1a binds to the *COMT1* (encoding Caffeic acid O-methyltransferase 1) promoter, increasing melatonin synthesis and subsequent PC/GSH production for vacuolar Cd sequestration [40]. Similarly, flavonoids mitigate Cd stress through their superior antioxidant capacity [41,42]. In rice, Cd-induced OsNAC300 activates *OsCHS1* (encoding a key flavonoid biosynthesis enzyme) to enhance flavonoid-mediated antioxidant defense [43]. Correspondingly, overexpression of *GmWRKY172* in soybean promotes Cd tolerance and reduces seed Cd accumulation by upregulating the flavonoid biosynthetic network [20].

In summary, TFs mitigate Cd-induced oxidative stress by modulating enzymatic and non-enzymatic antioxidants. However, ROS reduction alone is insufficient; plants employ additional strategies (chelation, compartmentalization, transporter regulation, signaling, and damage repair) for comprehensive Cd detoxification.

Table 2. Transcription factors regulating the expression of genes related to non-enzymatic antioxidant synthesis.

Family	Plant	Heavy Metal (Primarily Cd)	Gene Name	Gene Function	Expression Site	Response to Cd (Inhibition/Induction)	Up/Downstream Genes	Role in Cd Tolerance	Role in Cd Accumulation	Reference
WRKY	Arabidopsis	Cd	<i>AtWRKY18</i> , <i>AtWRKY40</i> , <i>AtWRKY60</i>	Inhibit H ₂ S synthesis	/	Induced	<i>LCD</i> , <i>DCD</i> , <i>DCD2</i> , <i>DES</i> , <i>NFS2</i>	Reduced	/	[37]
NAC	Rice	Cd	<i>OsNAC300</i>	Increased pathogenesis-related (PR) protein and flavonoid synthesis	Root	Induced	<i>OsPR10a</i> , <i>OsPR10b</i> , <i>OsCHS1</i>	Enhanced	Unchanged	[43]
HSF	Sedum	Cd	<i>SpHsfA4c</i>	Increased GSH and AsA synthesis	/	Induced	/	Enhanced	Enhanced	[34]
HSF	Tomato	Cd	<i>HsfA1a</i>	Induces melatonin biosynthesis and heat shock protein (HSP) expression	/	Induced	<i>COMT1</i>	Enhanced	/	[40]

2.2. Chelation of Cd

Chelation of free Cd into stable complexes by molecules such as phytochelatins (PCs) and metallothioneins (MTs) significantly reduces its biological toxicity. Studies demonstrate that TF families including WRKY, MYB, bHLH, bZIP, and ZAT directly or indirectly activate genes involved in PC and MT synthesis, thereby enhancing plant tolerance and reducing Cd accumulation [44,45].

2.2.1. Regulation of Phytochelatin Synthesis

PCs are cysteine-rich small peptides that bind metals via thiol groups. Their synthesis is induced by various metals, primarily facilitating detoxification of metals with high affinity for -SH groups, such as Cd, As (III), Zn, Hg, Pb, and Cu [46]. The glutathione-dependent PC synthesis pathway is critical for Cd tolerance in plant [47]. Reduced glutathione (GSH) serves as the precursor for PCs. Phytochelatin synthase 1 (PCS1) and PCS2 play key roles in PC synthesis, while γ -glutamylcysteine synthetase (GSH1) and glutathione synthase (GSH2) are essential for GSH production [45,48].

Under Cd stress, TFs enhance plant Cd chelation capacity by regulating key genes involved in GSH and PC synthesis, significantly improving Cd tolerance (Table 3). For instance, in *Arabidopsis*, Cd-induced AtWRKY45 upregulates *PCS1* and *PCS2* expression, increasing PC content, enhancing Cd tolerance, and promoting Cd accumulation. Additionally, AtWRKY45 facilitates Fe uptake, further mitigating Cd toxicity [45]. In contrast, AtWRKY12 negatively regulates Cd tolerance by binding to the *GSH1* promoter and suppressing its expression, indirectly inhibiting PC synthesis [49]. The zinc-finger TF ZAT6 positively regulates transcription of *GSH1*, *GSH2*, *PCS1*, and *PCS2*; its overexpression enhances Cd tolerance and accumulation in *Arabidopsis*, while loss-of-function mutants exhibit the opposite phenotype [47]. Both AtbZIP30 and AtERF2 bind to the promoter of glutathione S-transferase gene *AtGST1*, positively regulating its expression, improving ROS scavenging capacity and Cd chelation, and thereby enhancing Cd tolerance [50]. In rapeseed, TFs BnWRKY11, BnWRKY28, BnWRKY33, and BnWRKY75 are upregulated under Cd stress. Transcriptome analysis revealed significant enrichment of differentially expressed genes in glutathione metabolism pathways, particularly *BnPCS1*, *BnGSTU12*, and *BnGSTU5*, suggesting these TFs enhance Cd chelation and tolerance by promoting GSH and PC synthesis [51].

Table 3. Transcription factors regulating the expression of genes related to phytochelatin synthesis.

Family	Plant	Heavy Metal (Primarily Cd)	Gene Name	Gene Function	Expression Site	Response to Cd (Inhibition/Induction)	Up/Downregulated Gene
WRKY	Arabidopsis	Cd	<i>AtWRKY12</i>	Directly targets GSH1, inhibits expression of genes related to PC synthesis	Root, leaf, seed	Inhibited	GSH1
WRKY	Arabidopsis	Cd	<i>AtWRKY45</i>	Promotes expression of PC synthesis-related genes PCS1 and PCS2	Root, leaf	Induced	PCS1, PCS2
WRKY	Rape	Cd	<i>BnWRKY11</i> , <i>BnWRKY28</i> , <i>BnWRKY33</i> , <i>BnWRKY75</i>	Upregulates genes encoding GST and PCS, promoting formation of low molecular weight complexes (PC-Cd)	/	Induced	
MYB	Arabidopsis	Cd	<i>AtMYB75</i>	Increases GSH and PC content; binds promoters of ACBP2 and ABCC2, promoting chelation and compartmentalization	Leaf	Induced	ACBP2
bZIP	Arabidopsis	Cd	<i>AtbZIP30</i> , <i>AtERF2</i>	Regulates expression of glutathione S-transferase genes (AtGST)	/	/	AtGST
ZAT	Arabidopsis	Cd	<i>ZAT6</i>	Positively regulates genes involved in GSH1 and PC biosynthesis	/	Induced	ZAT6

2.2.2. Regulation of Metallothionein Synthesis

Metallothioneins (MTs) are low-molecular-weight, cysteine-rich proteins that play a vital role in heavy metal homeostasis and detoxification in plants [52]. They confer Cd tolerance through two primary mechanisms: high-affinity chelation of Cd^{2+} via their abundant thiol groups, and efficient scavenging of reactive oxygen species (ROS) to alleviate oxidative stress [53].

Functional studies in rice have provided direct evidence for these roles. For example, the expression of *OsMT1e* is strongly induced by Cd. Compared to wild-type controls, *OsMT1e*-overexpressing lines exhibit enhanced Cd tolerance, whereas *OsMT1e*-RNAi lines show inhibited growth, reduced chlorophyll content, and lower biomass under Cd stress. Furthermore, heterologous expression of *OsMT1e* in yeast confers a robust growth phenotype under Cd stress, consistent with its role in detoxification [54]. Similarly, the rice MT gene *OsMT2b* is co-induced by drought and Cd stress. Under drought, *OsMT2b* enhances tolerance by modulating the expression of ROS-scavenging genes. Its role in Cd tolerance is likely attributed to the direct binding of *OsMT2b* protein to Cd, thereby reducing the concentration of active Cd^{2+} [55].

Currently, systematic studies on TFs that regulate MT genes remain limited (Table 4), highlighting this as an emerging and promising research frontier. Known examples include the wheat A4-class heat shock TF gene *TaHsfA4a* and its rice ortholog *OsHsfA4a*, both of which are upregulated under Cd stress. Overexpression of *TaHsfA4a* enhances Cd tolerance in yeast and rice, while knockout of *OsHsfA4a* reduces tolerance. These TFs function by activating the expression of MT genes [56]. In Arabidopsis, AtMYB4 binds to the promoters of phytochelatin synthase (PCS) and metallothionein 1C (MT1C), positively regulating their expression to promote Cd chelation and increase tolerance [57]. Furthermore, in *Iris lactea* var. *chinensis*, the AP2/ERF transcription factor *IlAP2* mitigates Cd toxicity through a non-canonical mechanism. Instead of activating transcription, *IlAP2* physically interacts with the metallothionein *IlMT2a*. This interaction is proposed to reduce Cd accumulation and enhance tolerance by interfering with metal transport and modulating stress-responsive signaling pathways [58].

To systematically expand this regulatory network and advance explorations towards precision molecular breeding, future research should focus on the following interconnected directions: First, it is essential to deeply analyze the regulatory logic and key cis-regulatory elements (CREs)—such as metal response elements (MREs) and copper response elements (CuREs)—within MT gene promoters. Studies on promoters like *OsMT-I-4b* have already revealed their precise tissue specificity and responsiveness to multiple metals [59], laying the foundation for discovering upstream transcription factors and designing synthetic inducible systems [60]. Second, it is necessary to elucidate how transcription factors coordinate MT synthesis to balance the nutritional allocation of essential elements such as zinc with cadmium detoxification. Notably, *OsMT2b* and *OsMT2c*, which are highly expressed in the phloem of rice nodes, are crucial for zinc allocation to grains [61]. This suggests that transcriptional engineering of nodal MT expression may become a key strategy for maintaining mineral nutrition while reducing grain cadmium accumulation. Finally, cutting-edge technologies such as ATAC-seq should be integrated to map genome-wide chromatin accessibility and identify regulatory regions that become “open” under cadmium stress. Meanwhile, single-cell RNA sequencing (scRNA-seq) can help uncover endogenous, tissue-specific promoters with practical potential. Furthermore, CRISPR-mediated promoter engineering to drive root-specific expression of genes such as MTs could effectively “intercept” cadmium at critical sites, thereby minimizing its translocation to grains [60].

Table 4. Transcription factors regulating the expression of genes related to metallothionein synthesis.

Family	Plant	Heavy Metal (Primarily Cd)	Gene Name	Gene Function	Expression Site	Response to Cd (Inhibition/Induction)	Up/Downstream Genes	Role in Cd Tolerance	Role in Cd Accumulation	Reference
MYB	Arabidopsis	Cd	<i>AtMYB4</i>	Improves oxidative defense; increases <i>AtPCS1</i> and <i>AtMT1C</i> expression	Root, leaf	Induced	<i>PCS1, MT1C</i>	Enhanced	Enhanced	[57]
HSF	Wheat	Cd	<i>TaHsfA4a</i>	Enhances Cd tolerance in rice and yeast	/	Induced	<i>CUP1</i>	Enhanced	/	[56]
HSF	Rice	Cd	<i>OsHsfA4a</i>	Upregulates MT gene expression to enhance Cd tolerance	/	Induced	<i>OsMT-I-1a</i>	Enhanced	/	[56]
ZAT	Arabidopsis	Cd	<i>ZAT10</i>	Inhibits Cd uptake genes; positively regulates Cd chelation gene expression	/	Induced	<i>NAS1, NAS2, IRT2, MTP3</i>	Enhanced	Reduced	[62]
ERF	Iris lactea var. chinensis	Cd	<i>IlAP2</i>	Enhances Cd tolerance	/	Induced	<i>IlMT2a</i>	Enhanced	/	[58]

2.3. Compartmentalization (Sequestration)

Compartmentalization, the regulated transport and redistribution of Cd within plants, is a decisive process governing the final accumulation of Cd in grains. This process is orchestrated by diverse transcription factors that coordinate the sequestration of Cd into immobile compartments such as cell walls and vacuoles. Beyond cellular detoxification, this sequestration critically modulates the pool of free Cd ions available for xylem loading and subsequent translocation. As indicated by Yue et al., the efficacy of these sequestration mechanisms—which are governed by specific transcriptional networks in roots, nodes, and leaves—serves as a major checkpoint for grain safety. By transcriptionally enhancing tissue-specific “barrier” effects, plants can effectively restrict the flux of Cd destined for the grain during the reproductive stage [63]. Therefore, elucidating how transcription factors regulate these sequestration pathways presents a practical strategy for minimizing grain Cd accumulation without disrupting essential micronutrient homeostasis.

2.3.1. Cell Wall Binding

Plant cell walls, composed primarily of cellulose, hemicellulose, pectin, and lignin, exhibit strong adsorption capacity for Cd. The root cell wall serves as the primary physical barrier against heavy metal stress (e.g., Cd) [64]. Following Cd entry into roots, a significant fraction binds to cell wall components, limiting cytoplasmic influx and reducing phytotoxicity [65]. Hemicellulose constitutes a major Cd-binding site [66]. Notably, Cd-inducible *OsCDT1* in rice encodes a cysteine-rich protein localized to the plasma membrane and cell wall, which chelates Cd at the cell surface, restricting intracellular entry and enhancing Cd tolerance while reducing accumulation [67].

Transcription factors induce genes involved in cell wall biosynthesis, strengthening Cd sequestration capacity and minimizing cellular damage (Table 5). In *Arabidopsis*, *ANAC004* knockout reduced cell wall-bound Cd by $\geq 19.6\%$ and hemicellulose-bound Cd by $\geq 28.3\%$, suggesting compromised Cd tolerance due to reduced sequestration [68]. *AtbZIP44* positively regulates *MAN7* (encoding the endo- β -mannanase), modulating mannose content in the cell wall and influencing Cd binding, thereby reducing Cd uptake and root-to-shoot translocation [69]. Lignin mitigates Cd toxicity through functional group interactions [70]. In maize, *ZmbHLH105* overexpression enhances activities of lignin biosynthesis enzymes (PAL, CAD, LAC, POD), promoting cell wall thickening and Cd binding capacity, ultimately increasing Cd tolerance [71].

Table 5. Transcription factors regulating the expression of cell wall synthesis-related genes.

Family	Plant	Heavy Metal (Primarily Cd)	Gene Name	Gene Function	Expression Site	Response to Cd (Inhibition/Induction)	Up/Downstream Genes	Role in Cd Tolerance	Role in Cd Accumulation	Reference
bHLH	Maize	Cd	<i>ZmbHLH105</i>	Binds promoters of <i>ZmNCED1/2</i> to regulate ABA biosynthesis for ROS scavenging; confers Cd tolerance via ABA-mediated lignin deposition and root cell wall thickening	Root, leaf	Induced	<i>ZmNCED1/2</i>	Enhanced	Reduced	[71]
bZIP	Arabidopsis	Cd	<i>AtbZIP44</i>	Regulates mannanase MAN7 activity, enhancing cell wall Cd fixation capacity	Root, stem	Induced	<i>AtMAN7</i>	Enhanced	Reduced	[69]
NAC	Arabidopsis	Cd	<i>AtNAC102</i>	Regulates cell wall pectin metabolism and Cd binding, conferring Cd tolerance in Arabidopsis	Root	Induced (root), unchanged (shoot)	<i>WAKL11</i>	Enhanced	Reduced	[72]
NAC	Arabidopsis	Cd	<i>ANAC004</i>	Enhances Cd cell wall fixation; induces Cd chelation and compartmentalization gene expression; downregulates Cd translocation genes, reducing root-to-shoot Cd transfer	Root, flower, silique	Induced	<i>CS1/2, NAS4, ABCC1/2/3, MTP1/3, IREG2, NRAMP3/4</i>	Enhanced	Reduced	[68]

2.3.2. Vacuolar Sequestration

Vacuolar sequestration is a pivotal Cd detoxification mechanism. Proton pumps establish a transmembrane proton gradient that drives transporters to actively transport cytosolic Cd or Cd-complexes into vacuoles, reducing cytoplasmic toxicity [73]. For instance, ABCC1/2 transporters in *Arabidopsis* sequester Cd-PCs complexes into vacuoles, significantly enhancing tolerance [13]. In rice, the tonoplast transporter OsHMA3 sequesters Cd into root vacuoles, limiting translocation to shoots and reducing grain Cd accumulation [74]. CRISPR/Cas9-generated *OsHMA3* knockout mutants exhibit heightened Cd sensitivity, reduced root Cd accumulation, and increased shoot Cd content, confirming OsHMA3-mediated root vacuolar sequestration enhances tolerance by restricting Cd translocation [74].

Specific TFs activated by Cd stress regulate downstream vacuolar transporter genes, enhancing Cd sequestration into vacuoles (Table 6). This process effectively lowers cytosolic Cd concentration and alleviates toxicity. In *Arabidopsis*, AtMYB75 overexpression increases GSH and PC levels and upregulates chelation/sequestration genes, enhancing tolerance and accumulation [44]. Co-overexpression of bHLH TFs (FIT, AtbHLH38, AtbHLH39) activates *HMA3*, *MTP3*, *IRT2*, and *IREG2*, alleviating Cd toxicity by maintaining stem Fe levels and increasing vacuolar Cd storage [75]. AtbHLH104 positively regulates four Cd detoxification genes (*IREG2*, *MTP3*, *HMA3*, *NAS4*); its knockout mutants are Cd-sensitive, while overexpression lines exhibit high root Cd accumulation, reduced shoot Cd, and enhanced tolerance [76]. Conversely, AtMYB43 negatively regulates tolerance by suppressing key Cd transporter genes (*HMA2*, *HMA4*), hindering xylem transport and vacuolar sequestration [77].

In rice, OsCS1 (allelic to OsMTP11) critically regulates the translocation of Cd from leaves to grains [73]. It is predominantly expressed in leaf vascular parenchyma cells, where it sequesters Cd into vacuoles via the OsVSR2-mediated TGN-PVC-vacuole trafficking pathway (OsVSR2 is a vacuole-sorting receptor protein). By actively “trapping” Cd within the leaf endomembrane system during vegetative growth, OsCS1 effectively prevents its phloem loading and subsequent translocation to grains after heading. The high efficiency of this sequestration mechanism in indica rice stems from a natural variation in the *OsCS1* promoter: a duplication of a G-box-like motif. This structural variation strengthens the binding of the transcription factor OsIRO2, leading to intensified transcriptional activation and upregulated *OsCS1* expression. Consequently, Cd sequestration in leaf vacuoles is maximized, which provides the genetic basis for the superior low-Cd accumulation trait characteristic of indica rice varieties [78].

Table 6. Transcription factors regulating the expression of vacuolar sequestration-related genes.

Family	Plant	Heavy Metal (Primarily Cd)	Gene Name	Gene Function	Expression Site	Response to Cd (Inhibition/Induction)	Up/Downstream Genes	Role in Cd Tolerance	Role in Cd Accumulation	Reference
MYB	Arabidopsis	Cd	<i>AtMYB43</i>	Downregulates <i>HMA2</i> , <i>HMA3</i> , and <i>HMA4</i> gene expression	Whole plant	Induced	<i>PRL1</i>	Reduced	Enhanced (root), Reduced (shoot)	[77]
bHLH	Arabidopsis	Cd, Fe	<i>AtbHLH38</i> , <i>AtbHLH39</i>	Maintains high iron levels via iron transport and nicotianamine accumulation	Root, stem	Induced	<i>HMA3</i> , <i>MTP3</i> , <i>IREG2</i> , <i>IRTN2</i> , <i>NAS1</i> , <i>NAS2</i>	Enhanced	/	[75]
bHLH	Arabidopsis	Cd, Fe	<i>AtbHLH104</i>	Positively regulates genes for heavy metal detoxification; inhibits root-to-shoot Cd translocation	/	/	<i>IREG2</i> , <i>MTP3</i> , <i>HMA3</i> , <i>NAS4</i>	Enhanced	Enhanced (root), Reduced (shoot)	[76]
bHLH	Rice	Cd, Mn	<i>OsIRO2</i>	Upregulates <i>OsCS1</i>	/	/	<i>OsCS1</i>	Enhanced	Reduced	[78]

2.4. Regulation of Transporter Activity

A variety of metal transporters are involved in Cd uptake from roots and its translocation to grains in rice. These include: Zinc/Iron-regulated transporter-like Proteins (ZIPs), Natural Resistance-Associated Macrophage Proteins (NRAMPs), Heavy Metal-transporting ATPases (HMAs), Metal Tolerance Proteins (MTPs), ATP-Binding Cassette transporters (ABCs), Cation Exchangers (CAXs), Yellow Stripe-Like proteins (YSLs), and Iron-Regulated Transporters (IRTs) [79–82]. Upon Cd stress, plants activate specific transcription factors (TFs) to modulate the activity of these transporters (Table 7). Based on their primary regulatory roles, these TFs can be categorized into three groups: those enhancing Cd efflux, those suppressing Cd influx, and those coordinating long-distance transport.

2.4.1. Enhancing Cd Efflux and Cellular Exclusion

A primary plant defense strategy is to activate efflux transporters that export Cd from the cytoplasm. For example, in *Arabidopsis*, AtWRKY13 upregulates *PDR8* expression, leading to enhanced Cd extrusion and improved tolerance [83]. Similarly, PyWRKY48 in poplar promotes Cd exclusion by inducing heavy metal transporters and antioxidant enzymes [84]. In pepper, Cd stress-induced CaMYB TFs increase the expression of transporter genes involved in maintaining cellular homeostasis [85]. By reducing intracellular Cd levels, these TFs constitute a first line of defense against Cd toxicity.

2.4.2. Suppressing Cd Influx and Root Uptake

Limiting Cd uptake at the root level is crucial for reducing overall plant accumulation. This is achieved mainly through transcriptional repression or post-translational regulation of influx transporters:

(1) Transcriptional repression: In rice, OsNAC15 binds to the ZDRE *cis*-element in the promoters of *OsZIP7* and *OsZIP10*, suppressing their transcription and thereby decreasing Cd accumulation in shoots [86]. In wheat, TaWRKY70, TaNAC22, and TaWRKY74 repress several Cd transporter genes while enhancing antioxidant defense systems [29,87,88]. Moreover, AemNAC2/3 from *Aegilops markgrafii* significantly lowers Cd accumulation in wheat by downregulating *TaNRAMP5* and *TaHMA2* expression [89].

(2) Post-translational regulation: In *Arabidopsis*, AtWRKY33 employs a distinct mechanism by activating *ATL31*, which encodes an E3 ubiquitin ligase. ATL31 promotes ubiquitination and degradation of the influx transporter IRT1, thereby blocking Cd entry into cells [90].

2.4.3. Regulating Long-Distance Transport and Grain Allocation

Transcription factors that control Cd translocation from roots to grains are particularly important for food safety. In wheat, TaWRKY22 activates the *TaCOPT3D* promoter, enhancing Cd fixation in roots and limiting the metal pool available for grain translocation [91]. In maize, ZmWRKY64 acts as a broad regulator that coordinates multiple genes—such as *ZmABCC4*, *ZmNRAMP5*, and *ZmHMA3*—to balance Cd translocation with reactive oxygen species scavenging [92].

In rice, OsNAC5 functions as a key regulatory switch for grain Cd accumulation: it activates *OsNRAMP1* to promote Cd uptake, and its knockout significantly reduces grain Cd levels [16]. Conversely, in cotton, the GhbHLH121-GhRCD-GhMYB44 module fine-tunes the transcription of *HMA* genes to regulate transport efficiency [93]. In potato, StWRKY6 enhances Cd transport and chelation, thereby reducing overall accumulation [94].

Table 7. Transcription factors regulating the expression of Cd transporter genes.

Family	Plant	Heavy Metal (Primarily Cd)	Gene Name	Gene Function	Expression Site	Response to Cd (Inhibition/Induction)	Up/Downstream Genes	Role in Cd Tolerance	Role in Cd Accumulation	Reference
WRKY	Arabidopsis	Cd	<i>AtWRKY13</i>	Binds promoter of transporter <i>PDR8</i> to pump out Cd	Whole plant	Induced	<i>PRD1, PRD2, PRD8</i>	Enhanced	Reduced	[83]
WRKY	Arabidopsis	Cd	<i>AtWRKY33</i>	Interacts with ATL31, ubiquitinates and promotes IRT1 degradation	Root, leaf, seed	Induced	<i>ATL31, IRT1</i>	Enhanced	Reduced	[90]
WRKY	Wheat	Cd	<i>TaWRKY22</i>	Binds TaCOPT3D, enhances <i>HMA3</i> expression	/	Induced	<i>TaCOPT3D</i>	Enhanced	Enhanced (root), Reduced (grain)	[91]
WRKY	Wheat	Cd	<i>TaWRKY70</i>	Downregulates <i>AtHMA3</i> , <i>AtNRAMP5</i> , <i>AtYSL3</i> , <i>AtIRT1</i>	Root, stem	Induced	<i>TaCAT5</i>	Enhanced	Enhanced (root), Reduced (shoot)	[29]
WRKY	Wheat	Cd	<i>TaWRKY74</i>	Affects expression of AsA-GSH synthesis genes and inhibits expression of Cd transporter genes	Root, leaf, stem	Induced	/	Enhanced	Reduced	[88]
WRKY	Poplar	Cd	<i>PyWRKY48</i> , <i>PyWRKY71</i> , <i>PyWRKY45</i>	Upregulates transporter, heavy metal-binding protein, and xylem protein gene activity	Root, leaf, stem	Induced	<i>PaABC</i> , <i>PaHIP</i> , <i>PaNFP</i> , <i>PaBSP</i>	Enhanced	Enhanced	[84]
WRKY	Maize	Cd	<i>ZmWRKY64</i>	Regulates ROS homeostasis; positively regulates transporters	Root, leaf	Induced	<i>ZMSRG7</i>	Enhanced	Reduced	[92]
WRKY	Potato	Cd	<i>StWRKY6</i>	Upregulates genes for Cd chelation, plant defense, transporters, photomorphogenesis, and auxin signaling	Root, leaf, stem	Induced	<i>ERF013</i> , <i>BBX20</i> , <i>BAM5</i> , <i>VSP2</i> , <i>ABCG1</i> , <i>PDF1.4</i>	Enhanced	Reduced	[94]
MYB	Pepper	Cd, Cu, Zn	<i>CaMYB</i>	MYB protein interacts with Cd transporters (e.g., HMA) to improve plant tolerance to heavy metals	/	Induced	/	/	/	[85]

bHLH	Cotton	Cd	<i>GhBHLH12</i>	Interacts with GhRCD1, binds to and relieves transcriptional repression of <i>GhMYB44</i> ; GhMYB44 further interacts with GhPYL8 and activates transcription of heavy metal transporter <i>GhHMA1</i> , affecting Cd transport efficiency and tolerance	/	/	<i>GhRCD1, GhMYB44, GhHMA1</i>	Reduced	Reduced	[93]
NAC	Rice	Cd	<i>OsNAC15</i>	Binds promoters of <i>OsZIP7</i> and <i>OsZIP10</i> , inhibiting their transcription	Root	Induced	<i>OsZIP7, OsZIP10</i>	Enhanced	Enhanced (root), Reduced (shoot)	[86]
NAC	Rice	Cd	<i>OsNAC5</i>	Upregulates <i>OsNRAMP1</i> and <i>OsLEA3</i>	Root	Induced	<i>OsNRAMP1</i>	Enhanced	Enhanced	[16]
NAC	Wheat	Cd	<i>AemNAC2, AemNAC3</i>	Inhibit expression of <i>TaNRAMP5</i>	Root, shoot	Induced	<i>TaNRAMP5</i>	Enhanced	Reduced	[88]
NAC	Wheat	Cd	<i>TaNAC22</i>	Reduces Cd transporter levels and enhances antioxidant enzyme system	Leaf	Induced	<i>TaHMA2, TaIRT2, TaLCT1, TaHMA3, TaNRAMP1, TaNRAMP5</i>	Enhanced	Reduced	[87]

2.5. Regulation of Signal Transduction Pathways and Integration of Stress Signaling

Transcription factors (TFs) act as pivotal downstream effectors in signal transduction pathways, playing a central role in coordinating Cd detoxification mechanisms and enhancing plant tolerance [15,95]. The regulatory process begins with the early perception of Cd stress. Cd signals are detected by membrane-localized sensor modules, such as G protein-coupled receptors (GPCRs), calcium channels, and glutamate receptor-like (GLR) channels.

These sensors rapidly trigger the production of secondary messengers, including Ca^{2+} , calmodulin (CaM), ROS, and phytohormones [19,95]. These messengers are then decoded by specialized signaling cascades, such as calcium-dependent protein kinases (CDPKs), CBL-interacting protein kinases (CIPKs), and calcineurin B-like proteins (CBLs) [15]. Specifically, certain CDPKs or mitogen-activated protein kinases (MAPKs) modulate the DNA-binding affinity or stability of downstream TFs through phosphorylation, thereby initiating precise transcriptional responses to Cd [19].

Notably, MAPK and SnRK2 (sucrose non-fermenting-1-related protein kinase 2) pathways serve as common “signaling hubs” that mediate crosstalk between Cd stress and other biotic or abiotic stresses [15,19]. Given the substantial overlap between Cd-induced ROS/ Ca^{2+} signals and those triggered by drought, salinity, or pathogen infection, TFs can integrate multiple environmental cues to optimize defense strategies [19]. For instance, under Cd-induced oxidative stress, the MAPK cascade coordinates synergistic defense against heavy metal toxicity and biological invasion by interacting with jasmonic acid (JA) and salicylic acid (SA) pathways, highlighting plant capacity for signal integration under combined stresses [19].

This signal integration mechanism has been demonstrated in several studies (Table 8). In Arabidopsis, AtMYB59 functions as a key molecular switch that negatively regulates growth and Cd tolerance by maintaining Ca^{2+} homeostasis and modulating Ca^{2+} signaling [95]. In soybean, MYBZ2 is regulated by NADPH oxidase-derived ROS, implicating it in early oxidative stress signaling [96]. In rice, SNAC1 enhances Cd tolerance by coordinating MAPK signaling with ABA-dependent pathways, linking heavy metal response to osmotic stress adaptation [97].

TFs also participate in phytohormone-mediated signaling. In Arabidopsis, AtMYB49 interacts with ABI5 to participate in ABA-mediated inhibition of Cd accumulation [17], whereas in wheat, TabHLH094 interacts with TaMYC8 and limits ethylene synthesis to suppress Cd uptake and reduce grain Cd content [98,99]. Collectively, the extensive interplay between TFs and multiple hormone pathways (e.g., ABA, ethylene, and JA) indicates that the Cd-responsive network is deeply integrated with broader plant growth and defense systems, enabling robust adaption to complex environmental fluctuations [19].

Table 8. Transcription factors regulating the expression of signal transduction-related genes.

Family	Plant	Heavy Metal (Primarily Cd)	Gene Name	Gene Function	Expression Site	Response to Cd (Inhibition/Induction)	Up/Downstream Genes	Role in Cd Tolerance	Role in Cd Accumulation	Reference
MYB	Arabidopsis	Cd	<i>AtMYB59</i>	Negatively regulates Ca ²⁺ homeostasis and signaling	Root, leaf	Induced	<i>CMLs, KIC, CAX1, ACA1</i>	Enhanced	/	[95]
MYB	Soybean	Cd	<i>MYBZ2</i>	/	/	Induced	/	Enhanced	/	[96]
MYB	Arabidopsis	Cd	<i>AtMYB49</i>	Interacts with ABI5, participates in ABA synthesis; activates <i>IRT1, HIPP22, HIPP44</i>	Root, flower, stem, bud	Induced	<i>ABI5, bHLH38, bHLH101, HIPP22, HIPP44</i>	Enhanced	Enhanced	[17]
bHLH	Wheat	Cd	<i>TabHLH094</i>	Regulates transcriptional activity of <i>TaMYBC8</i> to reduce ethylene production	Root, stem	Induced	<i>TaMYC8, ACF, ACO</i>	Enhanced	Reduced	[98]
ERF	Wheat	Cd	<i>TaMYC8</i>	Inhibits ethylene biosynthesis pathway	Root, stem	Inhibited	<i>TaERF6</i>	Reduced	Enhanced	[99]
NAC	Rice	Cd	<i>SNAC1</i>	Regulates mitogen-activated protein kinase (MAPK) signaling cascade	/	/	/	Enhanced	/	[97]

2.6. Regulation of DNA and Protein Damage Repair

Cd induces DNA and protein damage and endoplasmic reticulum (ER) stress. Low Cd concentrations can directly bind to DNA, causing damage such as base mismatches, insertions, deletions, and breaks [100]. Cd also disrupts protein stability, causing misfolding and loss of function [101]. The MutS protein complex (encoded by *MSH* genes) recognizes DNA mismatches and initiates mismatch repair (MMR), implicating it in plant Cd tolerance. In rice, *msh* mutants exhibit more severe growth inhibition under Cd stress than wild-type plants [102]. Cao et al. found that MSH2 and MSH6 perceive Cd-induced DNA damage, activating cell cycle checkpoint genes and triggering G2/M phase arrest to allow time for DNA repair. In *msh2* and *msh6* mutants, upregulation of cell cycle-related genes is attenuated, G2/M arrest is reduced, and root growth is more severely inhibited [103]. Under Cd stress, misfolded protein accumulation triggers the unfolded protein response (UPR), activating TFs and upregulating chaperone to restore proteostasis. Prolonged stress may lead UPR to induce programmed cell death (PCD), inhibiting growth [104]. In soybean, Cd stress activates the developmental cell death (DCD)/asparagine-rich protein (NRP) signaling cascade, inducing GmNAC81 and GmNAC30, which activate vacuolar processing enzyme (VPE) to trigger PCD. Overexpression of the ER chaperone BIP alleviates ER stress and cell death by suppressing UPR and DCD/NRP pathway [101].

TFs repair Cd-induced DNA and protein damage by regulating relevant gene expression (Table 9). In rice, OsE2F activates MSH target genes, promoting DNA damage repair [102]. OsREX1-S enhances Cd tolerance by improving DNA damage repair capacity [105]. In Arabidopsis, AtbZIP60 upregulates ER chaperone genes, promoting folding and degradation of misfolded proteins to restore ER homeostasis. Under severe Cd stress, UPR activates NAC089, initiating PCD. In *atbzip60* mutants, expression of ER stress and PCD-related genes is reduced, suppressing UPR-mediated PCD and enhancing Cd tolerance [104]. NtbZIP60 is involved in ER stress and UPRs, regulating Cd tolerance in tobacco [106].

In summary, TFs counter Cd stress by orchestrating a range of detoxification mechanisms, thereby enhancing plant Cd tolerance and modulating Cd allocation and accumulation. Beyond these predominant pathways, a subset of TFs employ alternative strategies to confer Cd tolerance, as exemplified in Table 10. For example, in Arabidopsis, AtERF1B and AtERF104 activate NRT1.8, promoting nitrate allocation to roots and subsequently enhancing Cd tolerance [107]. AtZAT17 interacts with MAC spliceosome components, affecting alternative splicing of Cd stress-responsive genes and negatively regulating Cd tolerance [108]. In common bean, PvMTF-1 binds to the *ASA2* promoter, increasing free tryptophan levels, which contributes to reduced Cd accumulation, and enhanced Cd tolerance [109]. In rice, OsMYB36 promotes Casparian strip formation, thereby restricting apoplastic Cd transport and reducing Cd accumulation [110]. These specialized mechanisms likely reflect evolutionary adaptations that enable different species to thrive in specific Cd-stressed environments. They function synergistically with the primary detoxification pathways, collectively fine-tuning the plant's response to enhance environmental adaptability.

Table 9. Transcription factors regulating the expression of DNA and protein damage repair-related genes.

Family	Plant	Heavy Metal (Primarily Cd)	Gene Name	Gene Function	Expression Site	Response to Cd (Inhibition/Induction)	Up/Downstream Genes	Role in Cd Tolerance	Role in Cd Accumulation	Reference
bZIP	Arabidopsis	Cd	<i>AtbZIP28</i> , <i>AtbZIP60</i>	Reduces UPR and PCD, thereby increasing Cd tolerance	/	Induced	<i>BIP3</i>	Enhanced	/	[104]
bZIP	Tobacco	Cd	<i>NtbZIP60</i>	Associated with ER stress	/	Induced	/	/	/	[106]
bZIP	Rice	Cd	<i>OsZIP39</i>	Activates defense protein OsCAL2 to increase Cd uptake; upregulates UPR	/	Induced	<i>OsCAL2</i>	Reduced	Enhanced	[111]
E2F	Rice	Cd	<i>OsE2F</i>	Interacts with OsMSHs, promotes recognition and correction of mismatched bases; inhibits DNA damage	/	Induced	<i>OsMSHs</i>	Enhanced	/	[102]
TFIIH	Rice	Cd	<i>OsREX1-S</i>	Enhances DNA excision repair, conferring tolerance to Cd and UV-induced damage	/	Induced	/	Enhanced	/	[105]

Table 10. Transcription factors involved in other regulatory mechanisms.

Family	Plant	Heavy Metal (Primarily Cd)	Gene Name	Gene Function	Expression Site	Response to Cd (Inhibition/Induction)	Up/Downstream Genes	Role in Cd Tolerance	Role in Cd Accumulation	Reference
WRKY	Rice	Cd	<i>OsWRKY71</i> , <i>OsTRAB-1</i>	Acts as nodal components in Cd signaling pathways	Root, leaf, stem, seed	Induced	/	/	/	[112]
MYB	Rice	Cd	<i>OsMYB36</i>	Regulates Casparian strip formation in plants	Root, leaf, stem, lemma, leaf sheath	/	<i>OsCASP</i> , <i>OsESB1</i>	/	Reduced	[110]
bHLH	Soybean	Cd, Fe	<i>ORG3</i>	Increases Fe transport rate but reduces Cd	Root	Induced	/	Enhanced	Enhanced (root),	[113]

				translocation from root to stem				Reduced (shoot)		
ERF	Arabidopsis	Cd	<i>AtERF1b</i> , <i>AtERF104</i>	Promotes nitrate assimilation and photosynthesis	/	/	<i>NRT1.8</i> , <i>NRT1.5</i>	Enhanced	/	[107]
HSF	Sedum	Cd	<i>SaHSFA4c</i>	Upregulates antioxidant enzymes and heat shock proteins (HSPs), reduces ROS accumulation	Root, leaf, stem	Induced	/	Enhanced	/	[114]
ZAT	Arabidopsis	Cd	<i>ZAT17</i>	Induces <i>IRT1</i> and <i>NRT2.1</i> expression; interacts with MAC splicing complex (PRL1, CDC5), affecting alternative splicing (AS) of multiple Cd response genes	Root, leaf	Induced	<i>IRT1</i> , <i>NRT2.1</i> , <i>HMA3</i> , <i>PCR1</i>	Reduced	/	[108]
ERF	Common bean	Cd	<i>PVMTF-1</i>	Activates tryptophan biosynthesis	/	Induced	<i>AsA2</i>	Enhanced	/	[109]

3. Practical Applications of Transcription Factors for Reducing Cd Accumulation in Rice

3.1. Genetic Engineering Strategies: From Direct Effectors to Network Regulators

Genetic engineering offers a dual-track strategy for developing low-Cd rice cultivars: the precise modification of downstream functional genes, or the systemic reconfiguration of master-regulatory networks [60,115].

3.1.1. Precision Engineering of Structural and Functional Genes

The most direct approach involves manipulating functional genes—primarily encoding transport proteins and chelators—to alter specific physiological processes. For example, *OsNRAMP5* knockout reduces Cd uptake while promoting root-to-shoot translocation. The impact on shoot Cd accumulation depends on environmental Cd concentration: at low Cd (0–5 μM), knockout significantly reduces uptake and accumulation; at high Cd (10–15 μM), reduced uptake is less pronounced but translocation persists, increasing shoot Cd. Regardless, *OsNRAMP5* knockout enhances Cd tolerance [116]. *OsLCT1* transports various cations; RNAi-mediated *OsLCT1* knockdown reduces phloem-mediated Cd transport to grains, decreasing grain Cd by 50% without compromising growth or essential metal content [117]. Defensins enhance metal tolerance; rice *CAL1* encodes a defensin-like protein that chelates Cd via cysteine residues and secretes it extracellularly, reducing cytosolic Cd while facilitating Cd loading into xylem sap. *CAL1*-Cd complexes cannot enter phloem, resulting in preferential Cd accumulation in stems/leaves and low grain Cd [118]. *OsTHi9* overexpression enhances cell wall Cd binding, reduces root-to-shoot translocation and grain Cd accumulation without compromising grain quality [118].

3.1.2. Systemic Reprogramming via Transcription Factors (TFs)

Unlike single transporters, TFs can reconfigure entire defense networks simultaneously. Recent studies show that TFs coordinately modulate Cd allocation and accumulation. For example, *OsNAC5* positively regulates Cd tolerance; *osnac5* mutants show significantly reduced Cd in grains and husks, while complementation restores near-WT levels [16]. *OsWRKY72* negatively regulates *OsGLP8-7*, reducing lignin synthesis and weakening cell wall Cd binding, increasing cytosolic Cd accumulation. *oswrky72* mutants exhibit lower whole-plant Cd concentrations and reduced root Cd uptake, whereas overexpression lines show higher uptake [119]. Cd-inducible *OsHB4* overexpression increases Cd translocation factor, elevates xylem sap Cd, and enhances shoot/grain Cd accumulation. Conversely, *OsHB4* RNAi lines accumulate more Cd in roots and less in shoots, with lower grain Cd [120]. Uclacyanin (*UCL23*) negatively regulates Cd tolerance by elevating ROS. *OsWRKY51* activates the *UCL23* promoter while suppressing its post-transcriptional repressor *miR528*, increasing ROS and reducing Cd tolerance. *OsWRKY51* overexpression elevates Cd in all tissues, whereas knockout reduces grain Cd by 36% without affecting essential elements or agronomic traits [121].

3.2. Advantages of TFs as Master Regulators: The “Added Value” for Rice Improvement

While transgenic approaches targeting specific genes successfully reduce grain Cd accumulation, single-gene manipulations often fail to address the complexity of plant Cd detoxification networks and may cause unintended effects. TFs function as master regulators of gene expression networks, offering distinct advantages:

(1) Coordinated multi-gene regulation: A single TF can activate or suppress multiple functional genes, forming synergistic networks that comprehensively regulate Cd uptake,

transport, detoxification, and accumulation. This “one-to-many” characteristic makes TFs pivotal for deciphering complex stress adaptation mechanisms [122]. For example, ANAC004 overexpression enhances root hemicellulose-mediated Cd binding while regulating multiple detoxification genes, reducing Cd influx, promoting chelation/vacuolar sequestration, elevating ABA levels, and boosting antioxidant enzyme activity [68]. Similarly, ZmbHLH105 enhances ABA biosynthesis, lignin deposition, and cell wall thickening while inhibiting root Cd uptake [71].

(2) Key signaling nodes: TFs reside at critical junctions between stress signal perception and physiological responses. Studying them illuminates early Cd signaling pathways. For instance, AtMYB59 negatively regulates growth and tolerance via Ca^{2+} homeostasis and signaling pathways [95]. Researching such “molecular switches” elucidates the complete “Cd perception-signaling-response” pathway.

(3) Cross-stress and developmental coordination: TFs optimize resource allocation and coordinate multi-stress responses. Many Cd-responsive TFs also regulate salinity/drought pathways. For example, OsNAC5 enhances Cd tolerance and activates *OsCCR10*, increasing root lignin and improving drought tolerance [123]. OsNAC15 enhances Cd tolerance while interacting with ABA biosynthesis genes, conferring drought and salinity tolerance [124]. This multifunctionality enables plants to integrate internal and external signals for maximal adaptive fitness.

3.3. TF-Driven Genotypic Variations in Cd Distribution

The genetic potential of TFs is naturally reflected in the genotypic variations among rice cultivars. Significant diversity in Cd accumulation and translocation provides a natural template for identifying key regulatory nodes. Comprehensive field and pot experiments show that Cd concentrations in rice organs (roots, stems, leaves, grains) can vary more than eightfold across cultivars [125]. Physiologically, resistant genotypes (e.g., ‘Xiushui 817’) exhibit a superior capacity to restrict Cd root-to-shoot mobility compared to susceptible ones (e.g., ‘Zheda 821’), especially under combined heavy metal stress [11]. These studies highlight that grain Cd is determined not only by total uptake but, more critically, by the root-to-shoot translocation factor and the stem-to-grain redistribution ratio during different growth stages [11,126].

Molecularly, these phenotypic variations are orchestrated by differential TF expression or activity. In resistant genotypes, Cd-responsive TFs (e.g., NAC, WRKY, MYB) are often induced more rapidly or exhibit higher baseline expression, leading to robust activation of antioxidant systems and transporter genes. For instance, in high-Cd-accumulating cultivars, TFs may more effectively upregulate *OsHMA3*, *OsCCX2*, *OsNRAMP5*, and *OsHMA9* to facilitate Cd uptake and translocation. Conversely, in low-Cd accumulators, TFs likely upregulate genes like *OsIRT1*, *OsPCR1*, and *OsMTP1* to hinder Cd absorption [126]. Furthermore, TF interactions with multiple metal ions (Cd, Pb, Cr, Cu) appear genotype-specific, suggesting that some varieties possess more sophisticated TF-mediated networks capable of integrating diverse stress signals to maintain mineral homeostasis [11]. Understanding these natural variations is essential for identifying superior alleles and devising precision breeding strategies to develop “safe” rice varieties for contaminated soils.

4. Summary and Future Perspectives

This review comprehensively explores plant Cd detoxification mechanisms and the pivotal regulatory roles of TFs (Figure 2). Upon root exposure, Cd is initially bound by negatively charged groups in the cell wall. The residual Cd that enters cells via non-selective ion channels triggers cytotoxicity. Elevated Cd and reactive oxygen species (ROS) then activate diverse TFs, which mitigate toxicity by coordinately regulating: (1)

Restriction of root uptake through enhanced Cd binding in the cell wall. (2) Modulation of transporters to inhibit Cd influx, promote efflux, and reduce root-to-shoot translocation. (3) Chelation and sequestration via the upregulation of phytochelatin/metallothionein synthesis and vacuolar compartmentalization. (4) ROS scavenging by enhancing enzymatic and non-enzymatic antioxidant systems. (5) Damage repair and systemic coordination by facilitating DNA/protein repair, nitrate assimilation, tryptophan/hormone synthesis, and integrating stress signaling pathways.

These interconnected mechanisms constitute a dynamic, TF-coordinated network. However, to bridge the gap between mechanistic discovery and practical crop improvement, future research must evolve from characterizing isolated regulatory modules toward a systems-level roadmap. This holistic vision is supported by three emerging technological pillars:

(1) Unveiling Precision Breeding Targets via Multi-omics Integration

The deep integration of multi-omics technologies—including phenomics, genomics, transcriptomics, proteomics, and metabolomics—is advancing Cd resistance research from single-gene characterization toward a systems-level “safe-by-design” breeding framework [127]. This approach enables the identification of “hub” TFs that orchestrate Cd-response networks, effectively overcoming functional redundancy within TF families. For example, multi-omics-based co-expression networks have revealed that mitostasis (mitochondrial homeostasis) is a conserved core hub in cross-species Cd responses, with bHLH family members acting as central regulators that coordinate ROS scavenging and energy metabolism to maintain cell viability [128]. High-resolution multi-omics further delineates tissue- and genotype-specific strategies: rice root tips exhibit higher Cd accumulation and greater abundance of transporters (e.g., OsNramp1, OsNramp5) compared to mature zones, reflecting TF-mediated dynamic regulation in specific tissues [129]. Comparative proteomics between cultivars (e.g., Indica and Japonica) shows that tolerant varieties maintain homeostasis by enhancing antioxidant defense and energy metabolism proteins [130]—differences ultimately orchestrated by variations in TF expression or binding affinity. In summary, the key TFs and metabolic modules revealed through multi-omics integration provide high-confidence targets for precisely screening low-Cd germplasm and designing ideal varieties with combined tolerance and low accumulation via genome editing.

(2) Decoding the Multidimensional Regulatory Hierarchy via Epigenetics

Plant responses to Cd are profoundly shaped by epigenetic modifications—chemical alterations to DNA and associated proteins (e.g., histones) that regulate gene expression without changing the DNA sequence. These modifications, including DNA methylation, histone modifications, non-coding RNAs (ncRNAs), and microRNA-encoded peptides (miPEPs), cooperatively form a multidimensional network that fine-tunes Cd accumulation and tolerance. For instance, the Microrchidia protein OsMORC6 dynamically regulates Cd uptake and tolerance by mediating DNA methylation; its knockout alters differentially methylated regions (DMRs) and affects cell-wall and redox-related genes, thereby reducing rice Cd tolerance [131]. ncRNAs and their derived peptides extend this regulation post-transcriptionally, often using TFs as functional hubs. Cd-induced miR535 negatively regulates accumulation by targeting the TF OsSPL7, which derepresses transporters such as OsNRAMP5 [132]. Conversely, the peptide miPEP156e, encoded by a primary miRNA, enhances miR156 expression to inhibit SPL TFs, reducing Cd influx transporters (e.g., OsNRAMP5, OsZIP1/3/9) while improving ROS scavenging [133]. In rice roots, lncRNAs respond to Cd stress by activating MAPK signaling, diterpenoid biosynthesis, or phenylpropanoid pathways, and interact with TFs to modulate hormone signaling [134]. This hierarchical framework—integrating epigenetic marks, ncRNAs, peptides, and core TFs—provides a novel theoretical basis for

designing multidimensional molecular modules to develop high-performance, low-Cd rice varieties.

(3) Precise Spatiotemporal Control of Cd Responses via Promoter Engineering

Future research must shift from constitutive overexpression to precise spatiotemporal control. A key strategy is developing inducible promoters that drive gene expression only under specific stimuli (e.g., hormones, chemicals, or Cd stress). These promoters contain *cis*-regulatory elements (CREs)—such as metal response elements (MREs), copper response elements (CuREs), or G-boxes—that recruit trans-acting factors under defined conditions. Such “molecular switches” maintain low baseline expression to minimize metabolic cost, while enabling strong, Cd-specific induction to precisely activate detoxification pathways [60].

Complementing inducible systems, tissue-specific promoters can sequester Cd in “gatekeeper” tissues to block grain translocation. A definitive example is expressing the vacuolar transporter OsHMA3 under the root-, node-, and stem-enriched OsHMA2 promoter. This targeted expression intercepts Cd at critical entry and redistribution checkpoints, reducing brown rice Cd to <10% of wild-type levels without compromising yield or mineral nutrition [135].

Moving forward, research should integrate these spatiotemporal strategies—e.g., using root- or phloem-specific promoters—to ensure precise localization of gene expression. Moreover, leveraging RNA-seq to identify endogenous rice promoters that respond robustly and specifically to Cd stress, and using them to drive functional genes, is a highly promising direction. This approach not only optimizes detoxification efficiency but also avoids the instability and ethical concerns associated with exogenous strong promoters, offering a sustainable and socially acceptable molecular toolkit for developing high-yielding, “Cd-safe” rice varieties.

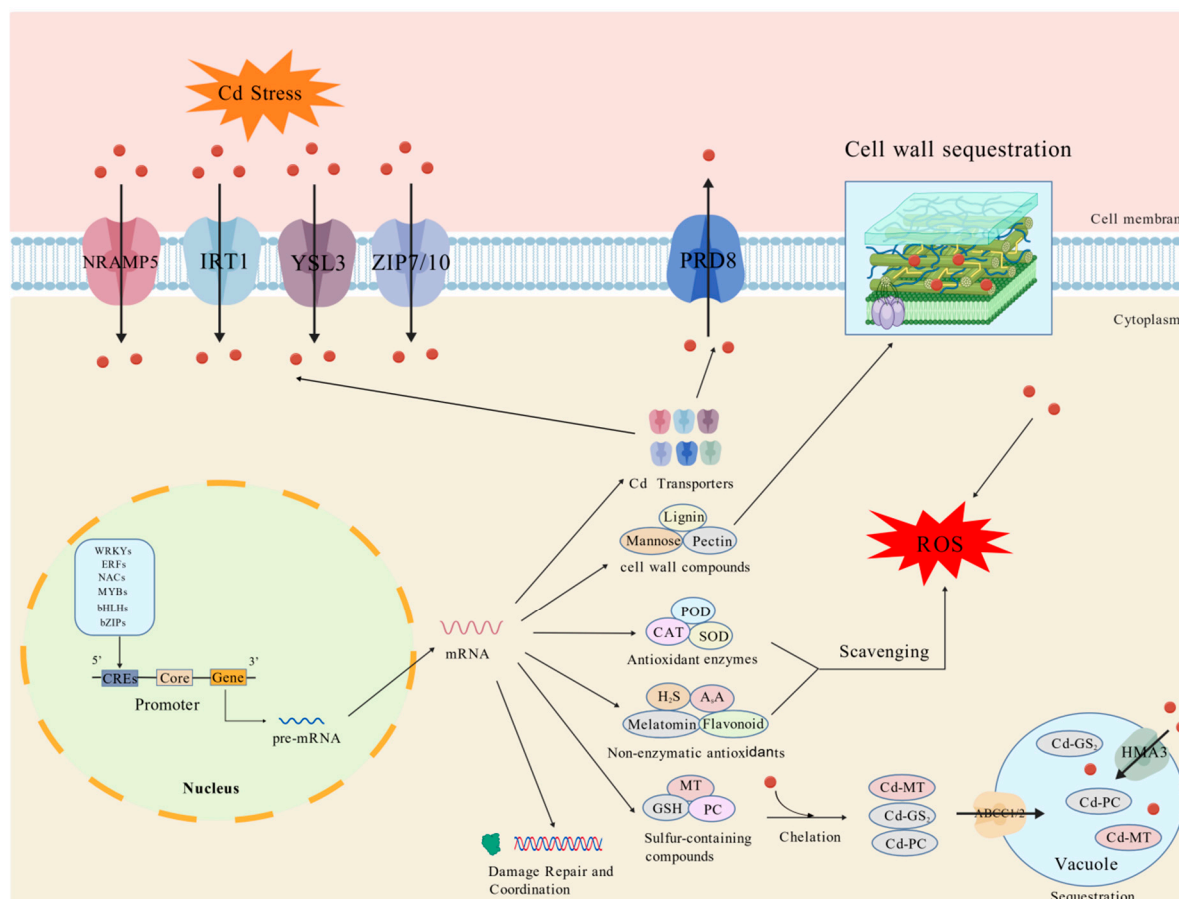


Figure 2. Schematic Diagram of Cd Uptake, Detoxification, and Regulatory Network in Plant Cells. Under Cd exposure, plants activate specific transcription factors (TFs) via signal transduction pathways, which precisely regulate the expression of downstream functional genes, forming a coordinated multi-modular core defense network. Key components of this network include: the antioxidant system, which alleviates oxidative damage by enhancing the activities of enzymes such as SOD, POD, and CAT, along with the synthesis of non-enzymatic antioxidants; chelation and compartmentalization, involving the production of phytochelatins (PCs) and metallothioneins (MTs), and the sequestration of Cd into vacuoles or its immobilization in the cell wall; regulation of Cd uptake and transport, through inhibition of Cd absorption and promotion of its efflux; as well as signaling cascades and repair of DNA and protein damage. Through the synergistic action of these finely tuned processes, plants achieve effective Cd detoxification and accumulation control, thereby enhancing tolerance while ensuring agricultural product safety. Created in BioGDP. com. Jiang, S. (2024) <https://base-img.rjmart.cn/image/diagram/cacgbc/42b020ba-f26c-4cc5-8bf2-6ee5761d29f1.png> (accessed on 12 January 2026). [136].

Author Contributions: Conceptualization, J.Y.; writing—original draft, Z.C. and J.Y.; writing—review and editing, J.Y., Z.C., X.X., Y.C. and Q.M.; visualization, Z.C.; supervision, J.Y.; funding acquisition, J.Y. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by grants from the National Natural Science Foundation of China (41877143) and Guangdong Basic and Applied Basic Research Foundation (2025A1515010989).

Data Availability Statement: No new data were created or analyzed in this study.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Xia, W.W.; Ghouri, F.; Zhong, M.H.; Bukhari, S.A.H.; Ali, S.; Shahid, M.Q. Rice and heavy metals: A review of cadmium impact and potential remediation techniques. *Sci. Total Environ.* **2024**, *957*, 177403. <https://doi.org/10.1016/j.scitotenv.2024.177403>.
2. Hou, D.Y.; Jia, X.Y.; Wang, L.W.; McGrath, S.P.; Zhu, Y.G.; Hu, Q.; Zhao, F.J.; Bank, M.S.; O'Connor, D.; Nriagu, J. Global soil pollution by toxic metals threatens agriculture and human health. *Science* **2025**, *388*, 316–321. <https://doi.org/10.1126/science.adr5214>.
3. Sui, F.Q.; Chang, J.D.; Tang, Z.; Liu, W.-J.; Huang, X.Y.; Zhao, F.J. Nramp5 expression and functionality likely explain higher cadmium uptake in rice than in wheat and maize. *Plant Soil* **2018**, *433*, 377–389.
4. Shi, Z.; Carey, M.; Meharg, C.; Williams, P.N.; Signes-Pastor, A.J.; Triwardhani, E.A.; Pandiangan, F.I.; Campbell, K.; Elliott, C.; Marwa, E.M.; et al. Rice Grain Cadmium Concentrations in the Global Supply-Chain. *Expo. Health.* **2020**, *12*, 869–876.
5. Wang, P.; Chen, H.; Kopittke, P.M.; Zhao, F.J. Cadmium contamination in agricultural soils of China and the impact on food safety. *Environ. Pollut.* **2019**, *249*, 1038–1048.
6. Genchi, G.; Sinicropi, M.S.; Lauria, G.; Carocci, A.; Catalano, A. The Effects of Cadmium Toxicity. *Int. J. Environ. Res. Public Health.* **2020**, *17*, 3782.
7. Nishijo, M.; Nakagawa, H.; Suwazono, Y.; Nogawa, K.; Kido, T. Causes of death in patients with Itai-itai disease suffering from severe chronic cadmium poisoning: A nested case-control analysis of a follow-up study in Japan. *BMJ Open* **2017**, *7*, e015694.
8. Smiri, M.; Chaoui, A.; El Ferjani, E. Respiratory metabolism in the embryonic axis of germinating pea seed exposed to cadmium. *J. Plant Physiol.* **2009**, *166*, 259–269.
9. Rizwan, M.; Ali, S.; Adrees, M.; Rizvi, H.; Zia-Ur-Rehman, M.; Hannan, F.; Qayyum, M.F.; Hafeez, F.; Ok, Y.S. Cadmium stress in rice: Toxic effects, tolerance mechanisms, and management: A critical review. *Environ. Sci. Pollut. Res.* **2016**, *23*, 17859–17879.
10. Li, S.; Yu, J.L.; Zhu, M.J.; Zhao, F.G.; Luan, S. Cadmium impairs ion homeostasis by altering K⁺ and Ca²⁺ channel activities in rice root hair cells. *Plant Cell Environ* **2012**, *35*, 1998–2013.
11. Xie, L.P.; Hao, P.F.; Cheng, Y.; Ahmed, I.M.; Cao, F.B. Effect of combined application of lead, cadmium, chromium and copper on grain, leaf and stem heavy metal contents at different growth stages in rice. *Ecotoxicol. Environ. Safe.* **2018**, *162*, 71–76.
12. Yang, G.L.; Zheng, M.M.; Tan, A.J.; Liu, Y.T.; Feng, D.; Lv, S.M. Research on the Mechanisms of Plant Enrichment and Detoxification of Cadmium. *Biology* **2021**, *10*, 544.

13. Lv, Q.Y.; Han, M.L.; Gao, Y.Q.; Zhang, C.Y.; Wang, Y.L.; Chao, Z.F.; Zhong, L.Y.; Chao, D.Y. Sec24C mediates a Golgi-independent trafficking pathway that is required for tonoplast localisation of ABCC1 and ABCC2. *New Phytol.* **2022**, *235*, 1486–1500.
14. Shumayla; Tyagi, S.; Sharma, Y.; Madhu; Sharma, A.; Pandey, A.; Singh, K.; Upadhyay, S.K. Expression of TaNCL2-A ameliorates cadmium toxicity by increasing calcium and enzymatic antioxidants activities in arabidopsis. *Chemosphere* **2023**, *329*, 138636.
15. Khan, S.A.; Li, M.Z.; Wang, S.M.; Yin, H.J. Revisiting the Role of Plant Transcription Factors in the Battle against Abiotic Stress. *Int. J. Mol. Sci.* **2018**, *19*, 1634.
16. Hu, S.B.; Chen, J.F.; Wang, H.; Ji, E.; Su, X.X.; Zhu, M.Y.; Xiang, X.Y.; Gong, L.; Zhou, Q.; Xiao, X.; et al. The transcription factor OsNAC5 regulates cadmium accumulation in rice. *Ecotox. Environ. Safe.* **2024**, *285*, 117102.
17. Zhang, P.; Wang, R.L.; Ju, Q.; Li, W.Q.; Tran, L.S.P.; Xu, J. The R2R3-MYB Transcription Factor MYB49 Regulates Cadmium Accumulation. *Plant Physiol.* **2019**, *180*, 529–542.
18. Hu, S.B.; Yu, Y.; Chen, Q.H.; Mu, G.M.; Shen, Z.G.; Zheng, L.Q. OsMYB45 plays an important role in rice resistance to cadmium stress. *Plant Sci.* **2017**, *264*, 1–8.
19. Thilakarathne, A.S.; Liu, F.; Zou, Z. Plant signaling hormones and transcription factors: Key regulators of plant responses to Growth, Development, and stress. *Plants* **2025**, *14*, 1070.
20. Xian, P.; Yang, Y.; Xiong, C.; Guo, Z.; Alam, I.; He, Z.; Zhang, Y.; Cai, Z.; Nian, H. Overexpression of GmWRKY172 enhances cadmium tolerance in plants and reduces cadmium accumulation in soybean seeds. *Front. Plant Sci.* **2023**, *14*, 1133892. <https://doi.org/10.3389/fpls.2023.1133892>.
21. Mansoor, S.; Ali, A.; Kour, N.; Bornhorst, J.; AlHarbi, K.; Rinklebe, J.; Abd El Moneim, D.; Ahmad, P.; Chung, Y.S. Heavy Metal Induced Oxidative Stress Mitigation and ROS Scavenging in Plants. *Plants* **2023**, *12*, 3003.
22. Luo, P.; Wu, J.; Li, T.-T.; Shi, P.; Ma, Q.; Di, D.W. An Overview of the Mechanisms through Which Plants Regulate ROS Homeostasis under Cadmium Stress. *Antioxidants* **2024**, *13*, 1174.
23. Kaur, R.; Das, S.; Bansal, S.; Singh, G.; Sardar, S.; Dhar, H.; Ram, H. Heavy metal stress in rice: Uptake, transport, signaling, and tolerance mechanisms. *Physiol. Plant* **2021**, *173*, 430–448.
24. Wu, X.L.; Chen, Q.; Chen, L.L.; Tian, F.F.; Chen, X.X.; Han, C.Y.; Mi, J.X.; Lin, X.Y.; Wan, X.Q.; Jiang, B.B.; et al. A WRKY transcription factor, PyWRKY75, enhanced cadmium accumulation and tolerance in poplar. *Ecotoxicol. Environ. Safe.* **2022**, *239*, 113630.
25. Wang, Y.Y.; Wu, J.; Li, J.H.; Liu, B.C.; Wang, D.; Gao, C.Q. The R2R3-MYB transcription factor ThRAX2 recognized a new element MYB-T (CTTCCA) to enhance cadmium tolerance in *Tamarix hispida*. *Plant Sci.* **2023**, *329*, 111574.
26. Gao, W.; Liu, B.; Phetmany, S.; Li, J.; Wang, D.; Liu, Z.; Gao, C. ThDIV2, an R-R-type MYB transcription factor of *Tamarix hispida*, negatively regulates cadmium stress by modulating ROS homeostasis. *Environ. Exp. Bot.* **2023**, *214*, 105453.
27. Wang, Y.; Gao, C.; Liang, Y.; Wang, C.; Yang, C.; Liu, G. A novel bZIP gene from *Tamarix hispida* mediates physiological responses to salt stress in tobacco plants. *J. Plant Physiol.* **2010**, *167*, 222–230.
28. Hong, C.Y.; Cheng, D.; Zhang, G.Q.; Zhu, D.D.; Chen, Y.H.; Tan, M.P. The role of ZmWRKY4 in regulating maize antioxidant defense under cadmium stress. *Biochem. Biophys. Res. Commun.* **2017**, *482*, 1504–1510.
29. Jia, Z.Z.; Li, M.Z.; Wang, H.C.; Zhu, B.; Gu, L.; Du, X.Y.; Ren, M.J. TaWRKY70 positively regulates TaCAT5 enhanced Cd tolerance in transgenic Arabidopsis. *Environ. Exp. Bot.* **2021**, *190*, 104591.
30. Djemal, R.; Khoudi, H. The ethylene-responsive transcription factor of durum wheat, TdSHN1, confers cadmium, copper, and zinc tolerance to yeast and transgenic tobacco plants. *Protoplasma* **2022**, *259*, 19–31.
31. Shalmani, A.; Ullah, U.; Muhammad, I.; Zhang, D.; Sharif, R.; Jia, P.; Saleem, N.; Gul, N.; Rakhmanova, A.; Tahir, M.M.; et al. The TAZ domain-containing proteins play important role in the heavy metals stress biology in plants. *Environ. Res.* **2021**, *197*, 111030.
32. Wang, H.N.; Li, J.X.; Liu, X.Y.; Gu, L.; Zhu, B.; Wang, H.C.; Du, X.Y. The SbWRKY54-SbHKT2b transcriptional cascade confers cadmium stress tolerance in sorghum. *Environ. Exp. Bot.* **2023**, *214*, 105478.
33. Yan, C.X.; Feng, B.; Zhao, Z.Y.; Zhang, Y.; Yin, K.X.; Liu, Y.; Zhang, X.M.; Liu, J.; Li, J.; Zhao, R.; et al. Populus euphratica R2R3-MYB transcription factor RAX2 binds ANN1 promoter to increase cadmium enrichment in Arabidopsis. *Plant Sci.* **2024**, *344*, 112082.
34. Yu, M.; He, Z.; Li, S.; Lu, Z.; Chen, J.; Qu, T.; Xu, J.; Qiu, W.; Han, X.; Zhuo, R. SpHsfA4c from *Sedum plumbizincicola* Enhances Cd Tolerance by the AsA–GSH Pathway in Transgenic *Populus × canescens*. *Agronomy* **2023**, *13*, 760. <https://doi.org/10.3390/agronomy13030760>.

35. Mostofa, M.G.; Rahman, A.; Ansary, M.M.U.; Watanabe, A.; Fujita, M.; Tran, L.S.P. Hydrogen sulfide modulates cadmium-induced physiological and biochemical responses to alleviate cadmium toxicity in rice. *Sci. Rep.* **2015**, *5*, 14078.
36. Tabassum, R.; Jeong, N.Y.; Jung, J. Therapeutic importance of hydrogen sulfide in age-associated neurodegenerative diseases. *Neural Regen. Res.* **2020**, *15*, 653–662.
37. Liu, Z.Q.; Fang, H.H.; Pei, Y.X.; Jin, Z.P.; Zhang, L.P.; Liu, D.M. WRKY transcription factors down-regulate the expression of H₂S-generating genes, LCD and DES in *Arabidopsis thaliana*. *Sci. Bull.* **2015**, *60*, 995–1001.
38. Ni, J.; Wang, Q.J.; Shah, F.A.; Liu, W.B.; Wang, D.D.; Huang, S.W.; Fu, S.L.; Wu, L.F. Exogenous Melatonin Confers Cadmium Tolerance by Counterbalancing the Hydrogen Peroxide Homeostasis in Wheat Seedlings. *Molecules* **2018**, *23*, 799. <https://doi.org/10.3390/molecules23040799>.
39. Gu, Q.; Wang, C.; Xiao, Q.; Chen, Z.; Han, Y. Melatonin Confers Plant Cadmium Tolerance: An Update. *Int. J. Mol. Sci.* **2021**, *22*, 11704.
40. Cai, S.Y.; Zhang, Y.; Xu, Y.P.; Qi, Z.Y.; Li, M.Q.; Ahammed, G.J.; Xia, X.J.; Shi, K.; Zhou, Y.H.; Reiter, R.J.; et al. HsfA1a upregulates melatonin biosynthesis to confer cadmium tolerance in tomato plants. *J. Pineal Res.* **2017**, *62*, e12387.
41. Hernández, I.; Alegre, L.; Van Breusegem, F.; Munné-Bosch, S. How relevant are flavonoids as antioxidants in plants? *Trends Plant Sci.* **2009**, *14*, 125–132.
42. Dias, M.C.; Pinto, D.C.G.A.; Silva, A.M.S. Plant Flavonoids: Chemical Characteristics and Biological Activity. *Molecules* **2021**, *26*, 5377. <https://doi.org/10.3390/molecules26175377>.
43. Hu, S.; Shinwari, K.I.; Song, Y.; Xia, J.; Xu, H.; Du, B.; Luo, L.; Zheng, L. OsNAC300 Positively Regulates Cadmium Stress Responses and Tolerance in Rice Roots. *Agronomy* **2021**, *11*, 95. <https://doi.org/10.3390/agronomy11010095>.
44. Zheng, T.; Lu, X.; Yang, F.; Zhang, D. Synergetic modulation of plant cadmium tolerance via MYB75-mediated ROS homeostasis and transcriptional regulation. *Plant Cell Reports.* **2022**, *41*, 1515–1530.
45. Li, F.; Deng, Y.; Liu, Y.; Mai, C.; Xu, Y.; Wu, J.; Zheng, X.; Liang, C.; Wang, J. Arabidopsis transcription factor WRKY45 confers cadmium tolerance via activating PCS1 and PCS2 expression. *J. Hazard. Mater.* **2023**, *460*, 132496.
46. Seregin, I.V.; Kozhevnikova, A.D. Phytochelatins: Sulfur-Containing Metal(loid)-Chelating Ligands in Plants. *Int. J. Mol. Sci.* **2023**, *24*, 2430. <https://doi.org/10.3390/ijms24032430>.
47. Chen, J.; Yang, L.B.; Yan, X.X.; Liu, Y.L.; Wang, R.; Fan, T.T.; Ren, Y.B.; Tang, X.F.; Xiao, F.M.; Liu, Y.S.; et al. Zinc-Finger Transcription Factor ZAT6 Positively Regulates Cadmium Tolerance through the Glutathione-Dependent Pathway in Arabidopsis. *Plant Physiol.* **2016**, *171*, 707–719.
48. Hasanuzzaman, M.; Nahar, K.; Anee, T.I.; Fujita, M. Glutathione in plants: Biosynthesis and physiological role in environmental stress tolerance. *Physiol. Mol. Biol. Plants* **2017**, *23*, 249–268.
49. Han, Y.; Fan, T.; Zhu, X.; Wu, X.; Ouyang, J.; Jiang, L.; Cao, S. WRKY12 represses GSH1 expression to negatively regulate cadmium tolerance in Arabidopsis. *Plant Mol. Biol.* **2019**, *99*, 149–159.
50. Kouno, T.; Ezaki, B. Multiple regulation of Arabidopsis AtGST11 gene expression by four transcription factors under abiotic stresses. *Physiol. Plant.* **2013**, *148*, 97–104.
51. Ding, Y.R.; Jian, H.J.; Wang, T.Y.; Di, F.F.; Wang, J.; Li, J.N.; Liu, L.Z. Screening of candidate gene responses to cadmium stress by RNA sequencing in oilseed rape (*Brassica napus* L.). *Environ. Sci. Pollut. Res.* **2018**, *25*, 32433–32446.
52. Bourdineaud, J.P.; Baudrimont, M.; Gonzalez, P.; Moreau, J.L. Challenging the model for induction of metallothionein gene expression. *Biochimie* **2006**, *88*, 1787–1792.
53. Hassinen, V.H.; Tervahauta, A.I.; Schat, H.; Kärenlampi, S.O. Plant metallothioneins—Metal chelators with ROS scavenging activity? *Plant Biol.* **2011**, *13*, 225–232.
54. Rono, J.K.; Wang, L.L.; Wu, X.C.; Cao, H.W.; Zhao, Y.N.; Khan, I.U.; Yang, Z.M. Identification of a new function of metallothionein-like gene OsMT1e for cadmium detoxification and potential phytoremediation. *Chemosphere* **2021**, *265*, 129136.
55. Chen, Y.X.; He, Y.; Pan, Y.B.; et al. Involvement of the metallothionein gene OsMT2b in Drought and Cadmium ions stress in Rice. *Rice* **2024**, *17*, 63.
56. Shim, D.H.; Hwang, J.U.; Lee, J.H.; Lee, S.C.; Choi, Y.J.; An, G.H.; Martinoia, E.; Lee, Y.S. Orthologs of the Class A4 Heat Shock Transcription Factor HsfA4a Confer Cadmium Tolerance in Wheat and Rice. *Plant Cell* **2009**, *21*, 4031–4043.
57. Agarwal, P.; Mitra, M.; Banerjee, S.; Roy, S. MYB4 transcription factor, a member of R2R3-subfamily of MYB domain protein, regulates cadmium tolerance via enhanced protection against oxidative damage and increases expression of PCS1 and MT1C in Arabidopsis. *Plant Sci.* **2020**, *297*, 110501.
58. Wang, Z.Q.; Ni, L.J.; Liu, L.Q.; Yuan, H.; Gu, C. IAP2, an AP2/ERF Superfamily Gene, mediates cadmium tolerance by interacting with IIMT2a in *Iris lactea* var. *Chinensis*. *Plants* **2023**, *12*, 12040823.

59. Dong, C.J.; Wang, Y.; Yu, S.S.; Liu, J.Y. Characterization of a novel rice metallothionein gene promoter: Its tissue specificity and heavy metal responsiveness. *J. Integr. Plant Biol.* **2010**, *52*, 914–924.
60. Xu, X.X.; Mo, Q.X.; Cai, Z.B.; Jiang, Q.; Zhou, D.M.; Yi, J.C. Promoters, Key Cis-Regulatory Elements, and Their Potential Applications in Regulation of Cadmium (Cd) in Rice. *Int. J. Mol. Sci.* **2024**, *25*, 13237.
61. Lei, G.J.; Yamaji, N.; Ma, J.F. Two metallothionein genes highly expressed in rice nodes are involved in distribution of Zn to the grain. *New Phytol.* **2021**, *229*, 1007–1120.
62. Dang, F.F.; Li, Y.J.; Wang, Y.F.; Lin, J.H.; Du, S.X.; Liao, X.Y. ZAT10 plays dual roles in cadmium uptake and detoxification in Arabidopsis. *Front. Plant Sci.* **2022**, *13*, 994100.
63. Yue, J.T.; Zhang, N.; Wu, D.Z.; Gao, F. Molecular insights into cadmium transport and micronutrient crosstalk in rice: Towards minimizing grain Cd. *J. Integr. Plant Biol.* **2025**. <https://doi.org/10.1111/jipb.70094>.
64. Loix, C.; Huybrechts, M.; Vangronsveld, J.; Gielen, M.; Keunen, E.; Cuypers, A. Corrigendum: Reciprocal Interactions between Cadmium-Induced Cell Wall Responses and Oxidative Stress in Plants. *Front. Plant Sci.* **2018**, *9*, 00391.
65. Zhang, J.L.; Zhu, Y.C.; Yu, L.J.; Yang, M.; Zou, X.; Yin, C.X.; Lin, Y.J. Research Advances in Cadmium Uptake, Transport and Resistance in Rice (*Oryza sativa* L.). *Cells* **2022**, *11*, 569. <https://doi.org/10.3390/cells11030569>.
66. Zhu, X.F.; Wang, Z.W.; Dong, F.; Lei, G.J.; Shi, Y.Z.; Li, G.X.; Zheng, S.J. Exogenous auxin alleviates cadmium toxicity in Arabidopsis thaliana by stimulating synthesis of hemicellulose 1 and increasing the cadmium fixation capacity of root cell walls. *J. Hazard. Mater.* **2013**, *263*, 398–403.
67. Kuramata, M.; Masuya, S.; Takahashi, Y.; Kitagawa, E.; Inoue, C.; Ishikawa, S.; Youssefian, S.; Kusano, T. Novel Cysteine-Rich Peptides from Digitaria ciliaris and Oryza sativa Enhance Tolerance to Cadmium by Limiting its Cellular Accumulation. *Plant Cell Physiol.* **2009**, *50*, 106–117.
68. Meng, Y.T.; Zhang, X.L.; Wu, Q.; Shen, R.F.; Zhu, X.F. Transcription factor ANAC004 enhances Cd tolerance in Arabidopsis thaliana by regulating cell wall fixation, translocation and vacuolar detoxification of Cd, ABA accumulation and antioxidant capacity. *J. Hazard. Mater.* **2022**, *436*, 129121.
69. Wu, Q.; Meng, Y.T.; Feng, Z.H.; Shen, R.F.; Zhu, X.F. The endo-beta mannase MAN7 contributes to cadmium tolerance by modulating root cell wall binding capacity in Arabidopsis thaliana. *J. Integr. Plant Biol.* **2023**, *65*, 1670–1686.
70. Parrotta, L.; Guerriero, G.; Sergeant, K.; Cai, G.; Hausman, J.F. Target or barrier? The cell wall of early- and later-diverging plants vs. cadmium toxicity: Differences in the response mechanisms. *Front. Plant Sci.* **2015**, *6*, 00133.
71. Meng, Y.Z.; Li, M.Y.; Guo, Z.T.; Chen, J.F.; Wu, J.Y.; Xia, Z.L. The transcription factor ZmbHLH105 confers cadmium tolerance by promoting abscisic acid biosynthesis in maize. *J. Hazard. Mater.* **2024**, *480*, 135826.
72. Han, G.H.; Huang, R.N.; Hong, L.H.; Xu, J.X.; Hong, Y.G.; Wu, Y.H.; Chen, W.W. The transcription factor NAC102 confers cadmium tolerance by regulating WAKL11 expression and cell wall pectin metabolism in Arabidopsis. *J. Integr. Plant Biol.* **2023**, *65*, 2262–2278.
73. Sharma, S.S.; Dietz, K.J.; Mimura, T. Vacuolar compartmentalization as indispensable component of heavy metal detoxification in plants. *Plant Cell Environ.* **2016**, *39*, 1112–1126.
74. Yan, H.J.; Jiao, X.Z.; Chen, Y.Y.; Liang, H.A.; Liang, W.H.; Liu, C.L. Knockout of OsHMA3 in an indica rice increases cadmium sensitivity and inhibits plant growth. *Plant Growth Regul.* **2024**, *103*, 635–646.
75. Wu, H.; Chen, C.; Du, J.; Liu, H.; Cui, Y.; Zhang, Y.; He, Y.; Wang, Y.; Chu, C.; Feng, Z.; et al. Co-Overexpression FIT with AtbHLH38 or AtbHLH39 in Arabidopsis-Enhanced Cadmium Tolerance via Increased Cadmium Sequestration in Roots and Improved Iron Homeostasis of Shoots. *Plant Physiol.* **2012**, *158*, 790–800.
76. Yao, X.N.; Cai, Y.R.; Yu, D.Q.; Liang, G. bHLH104 confers tolerance to cadmium stress in Arabidopsis thaliana. *J. Integr. Plant Biol.* **2018**, *60*, 691–702.
77. Zheng, P.; Cao, L.; Zhang, C.; Pan, W.; Wang, W.; Yu, X.; Li, Y.; Fan, T.; Miao, M.; Tang, X.; et al. MYB43 as a novel substrate for CRL4PRL1 E3 ligases negatively regulates cadmium tolerance through transcriptional inhibition of HMAs in Arabidopsis. *New Phytol.* **2022**, *234*, 884–901.
78. Liu, P.; Sun, L.; Zhang, Y.; Tan, Y.; Zhu, Y.; Peng, C.; Wang, J.; Yan, H.; Mao, D.; Liang, G.; et al. The metal tolerance protein OsMTP11 facilitates cadmium sequestration in the vacuoles of leaf vascular cells for restricting its translocation into rice grains. *Mol. Plant.* **2024**, *17*, 1733–1752.
79. Nakanishi, H.; Ogawa, I.; Ishimaru, Y.; Mori, S.; Nishizawa, N.K. Iron deficiency enhances cadmium uptake and translocation mediated by the Fe²⁺ transporters OsIRT1 and OsIRT2 in rice. *Soil Sci. Plant Nutr.* **2006**, *52*, 464–469.

80. Ram, H.; Kaur, A.; Gandass, N.; Singh, S.; Deshmukh, R.; Sonah, H.; Sharma, T.R. Molecular characterization and expression dynamics of MTP genes under various spatio-temporal stages and metal stress conditions in rice. *PLoS ONE* **2019**, *14*, e0217360. <https://doi.org/10.1371/journal.pone.0217360>.
81. Zou, W.L.; Chen, J.G.; Meng, L.J.; Chen, D.D.; He, H.H.; Ye, G.Y. The Rice Cation/H⁺ Exchanger Family Involved in Cd Tolerance and Transport. *Int. J. Mol. Sci.* **2021**, *22*, 8186.
82. Liu, C.; Wen, L.; Cui, Y.; Ahammed, G.J.; Cheng, Y. Metal transport proteins and transcription factor networks in plant responses to cadmium stress. *Plant Cell Rep.* **2024**, *43*, 218. <https://doi.org/10.1007/s00299-024-03303-x>.
83. Sheng, Y.B.; Yan, X.X.; Huang, Y.; Han, Y.Y.; Zhang, C.; Ren, Y.B.; Fan, T.T.; Xiao, F.M.; Liu, Y.S.; Cao, S.Q. The WRKY transcription factor, WRKY13, activates PDR8 expression to positively regulate cadmium tolerance in Arabidopsis. *Plant Cell Environ.* **2019**, *42*, 891–903.
84. Wu, X.; Chen, L.; Lin, X.; Chen, X.; Han, C.; Tian, F.; Wan, X.; Liu, Q.; He, F.; Chen, L.; et al. Integrating physiological and transcriptome analyses clarified the molecular regulation mechanism of PyWRKY48 in poplar under cadmium stress. *Int. J. Biol. Macromol.* **2023**, *238*, 124072.
85. Xie, Y.F.; Zhang, R.X.; Qin, L.J.; Song, L.L.; Zhao, D.G.; Xia, Z.M. Genome-wide identification and genetic characterization of the CaMYB family and its response to five types of heavy metal stress in hot pepper (*Capsicum annuum* cv. CM334). *Plant Physiol. Biochem.* **2022**, *170*, 98–109.
86. Zhan, J.H.; Zou, W.L.; Li, S.Y.Y.; Tang, J.C.; Lu, X.; Meng, L.J.; Ye, G.Y. OsNAC15 Regulates Tolerance to Zinc Deficiency and Cadmium by Binding to OsZIP7 and OsZIP10 in Rice. *Int. J. Mol. Sci.* **2022**, *23*, 11771.
87. Yu, Y.A.; Zhang, L. The wheat NAC transcription factor TaNAC22 enhances cadmium stress tolerance in wheat. *Cereal Res. Commun.* **2023**, *51*, 867–877.
88. Li, G.Z.; Zheng, Y.X.; Liu, H.T.; Liu, J.; Kang, G.Z. WRKY74 regulates cadmium tolerance through glutathione-dependent pathway in wheat. *Environ. Sci. Pollut. Res.* **2022**, *29*, 68191–68201.
89. Du, X.Y.; He, F.; Zhu, B.; Ren, M.J.; Tang, H. NAC transcription factors from *Aegilops markgrafii* reduce cadmium concentration in transgenic wheat. *Plant Soil.* **2020**, *449*, 39–50.
90. Zhang, C.; Tong, C.; Cao, L.; Zheng, P.; Tang, X.; Wang, L.; Miao, M.; Liu, Y.; Cao, S. Regulatory module WRKY33-ATL31-IRT1 mediates cadmium tolerance in Arabidopsis. *Plant Cell Environ.* **2023**, *46*, 1653–1670.
91. Liu, X.J.; Wang, H.C.; He, F.; Du, X.Y.; Ren, M.J.; Bao, Y.G. The TaWRKY22–TaCOPT3D Pathway Governs Cadmium Uptake in Wheat. *Int. J. Mol. Sci.* **2022**, *23*, 10379. <https://doi.org/10.3390/ijms231810379>.
92. Gu, L.; Hou, Y.; Sun, Y.; Chen, X.; Wang, G.; Wang, H.; Zhu, B.; Du, X. The maize WRKY transcription factor ZmWRKY64 confers cadmium tolerance in Arabidopsis and maize (*Zea mays* L.). *Plant Cell Rep.* **2024**, *43*, 44.
93. Wei, X.; Geng, M.H.; Yuan, J.C.; Zhan, J.J.; Liu, L.S.; Chen, Y.L.; Wang, Y.; Qin, W.Q.; Duan, H.Y.; Zhao, H.; et al. GhRCD1 promotes cotton tolerance to cadmium by regulating the GhbHLH12–GhMYB44–GhHMA1 transcriptional cascade. *Plant Biotechnol. J.* **2024**, *22*, 1777–1796.
94. Ram, H.; Kaur, A.; Gandass, N.; Singh, S.; Deshmukh, R.; Sonah, H.; Sharma, T.R.; Molecular He, G.D.; Saleem, M.; Deng, T.F.; et al. Unraveling the Mechanism of StWRKY6 in Potato (*Solanum tuberosum*)’s Cadmium Tolerance for Ensuring Food Safety. *Foods* **2023**, *12*, 2303.
95. Fasani, E.; DalCorso, G.; Costa, A.; Zenoni, S.; Furini, A. The Arabidopsis thaliana transcription factor MYB59 regulates calcium signalling during plant growth and stress response. *Plant Mol. Biol.* **2019**, *99*, 517–553.
96. Chmielowska-Bak, J.; Arasimowicz-Jelonek, M.; Izbiańska-Jankowska, K.; Frontasyeva, M.; Zinicovscaia, I.; Guianca-Varela, C.; Deckert, J. NADPH oxidase is involved in regulation of gene expression and ROS overproduction in soybean (*Glycine max* L.) seedlings exposed to cadmium. *Acta Soc. Bot. Pol.* **2017**, *86*, 3551–3568. <https://doi.org/10.5586/asbp.3551>.
97. Wang, B.; Zhang, M.; Zhang, J.; Huang, L.; Chen, X.; Jiang, M.; Tan, M. Profiling of rice Cd-tolerant genes through yeast-based cDNA library survival screening. *Plant Physiol. Biochem.* **2020**, *155*, 429–436.
98. Du, X.Y.; Fang, L.H.; Li, J.X.; Chen, T.J.; Cheng, Z.; Zhu, B.; Gu, L.; Wang, H.C. The TabHLH094–TaMYC8 complex mediates the cadmium response in wheat. *Mol. Breed.* **2023**, *43*, 57.
99. Wang, H.C.; Zuo, D.; Zhu, B.; Du, X.Y.; Gu, L. TaMYC8 regulates TaERF6 and inhibits ethylene synthesis to confer Cd tolerance in wheat. *Environ. Exp. Bot.* **2022**, *198*, 104854.
100. Filipič, M. Mechanisms of cadmium induced genomic instability. *Mutat. Res./Fundam. Mol. Mech. Mutagen.* **2012**, *733*, 69–77.
101. Quadros, I.P.S.; Madeira, N.N.; Lariato, V.A.P.; Saia, T.F.F.; Silva, J.C.; Soares, F.A.F.; Carvalho, J.R.; Reis, P.A.B.; Fontes, E.P.B.; Clarindo, W.R.; et al. Cadmium-mediated toxicity in plant cells is associated with the DCD/NRP-mediated cell death response. *Plant Cell Environ.* **2022**, *45*, 556–571.

102. Zheng, W.J.; Li, W.Q.; Peng, Y.; Shao, Y.; Tang, L.; Liu, C.T.; Zhang, D.; Zhang, L.J.; Li, J.H.; Luo, W.Z.; et al. E2Fs co-participate in cadmium stress response through activation of MSHs during the cell cycle. *Front. Plant Sci.* **2022**, *13*, 1068769.
103. Cao, X.; Wang, H.T.; Zhuang, D.F.; Zhu, H.; Du, Y.L.; Cheng, Z.B.; Cui, W.N.; Rogers, H.J.; Zhang, Q.R.; Jia, C.J.; et al. Roles of MSH2 and MSH6 in cadmium-induced G2/M checkpoint arrest in Arabidopsis roots. *Chemosphere* **2018**, *201*, 586–594.
104. De Benedictis, M.; Gallo, A.; Migoni, D.; Papadia, P.; Roversi, P.; Santino, A. Cadmium treatment induces endoplasmic reticulum stress and unfolded protein response in Arabidopsis thaliana. *Plant Physiol. Biochem.* **2023**, *196*, 281–290.
105. Kunihiro, S.; Kowata, H.; Kondou, Y.; Takahashi, S.; Matsui, M.; Berberich, T.; Youssefian, S.; Hidema, J.; Kusano, T. Overexpression of rice OsREX1-S, encoding a putative component of the core general transcription and DNA repair factor IIIH, renders plant cells tolerant to cadmium- and UV-induced damage by enhancing DNA excision repair. *Planta* **2014**, *239*, 1101–1111.
106. Xu, H.; Xu, W.; Xi, H.; Ma, W.; He, Z.; Ma, M. The ER luminal binding protein (BiP) alleviates Cd²⁺-induced programmed cell death through endoplasmic reticulum stress–cell death signaling pathway in tobacco cells. *J. Plant Physiol.* **2013**, *170*, 1434–1441.
107. Zhang, G.B.; Yi, H.Y.; Gong, J.M. The Arabidopsis Ethylene/Jasmonic Acid-NRT Signaling Module Coordinates Nitrate Reallocation and the Trade-Off between Growth and Environmental Adaptation. *Plant Cell* **2014**, *26*, 3984–3998.
108. Feng, Q.L.; Zhao, L.M.; Jiang, S.L.; Qiu, Y.X.; Zhai, T.T.; Yu, S.W.; Yang, W.; Zhang, S.X. The C2H2 family protein ZAT17 engages in the cadmium stress response by interacting with PRL1 in Arabidopsis. *J. Hazard. Mater.* **2024**, *465*, 133528.
109. Sun, N.; Liu, M.; Zhang, W.; Yang, W.; Bei, X.; Ma, H.; Qiao, F.; Qi, X. Bean Metal-Responsive Element-Binding Transcription Factor Confers Cadmium Resistance in Tobacco. *Plant Physiol.* **2015**, *167*, 1136–1148.
110. Wang, Z.G.; Zhang, B.L.; Chen, Z.W.; Wu, M.J.; Chao, D.; Wei, Q.X.; Xin, Y.F.; Li, L.Y.; Ming, Z.H.; Xia, J.X. Three OsMYB36 members redundantly regulate Casparian strip formation at the root endodermis. *Plant Cell* **2022**, *34*, 2948–2968.
111. Li, J.; Wang, L.Y.; Huang, H.C.; Yang, W.; Dai, G.Y.; Fang, Z.Q.; Zhao, J.L.; Xia, K.F.; Zeng, X.; He, M.L.; et al. Endoplasmic reticulum stress response modulator OsbZIP39 regulates cadmium accumulation via activating the expression of defensin-like gene OsCAL2 in rice. *J. Hazard. Mater.* **2024**, *476*, 135007.
112. Paul, S.; Roychoudhury, A. Transcriptome Profiling of Abiotic Stress-Responsive Genes During Cadmium Chloride-Mediated Stress in Two Indica Rice Varieties. *J. Plant Growth Regul.* **2018**, *37*, 657–667.
113. Xu, Z.L.; Liu, X.Q.; He, X.L.; Xu, L.; Huang, Y.H.; Shao, H.B.; Zhang, D.Y.; Tang, B.P.; Ma, H.X. The Soybean Basic Helix-Loop-Helix Transcription Factor ORG3-Like Enhances Cadmium Tolerance via Increased Iron and Reduced Cadmium Uptake and Transport from Roots to Shoots. *Front. Plant Sci.* **2017**, *8*, 01098.
114. Chen, S.S.; Yu, M.; Li, H.; Wang, Y.; Lu, Z.C.; Zhang, Y.X.; Liu, M.Y.; Qiao, G.R.; Wu, L.H.; Han, X.J.; et al. *SaHsfA4c* from *Sedum alfredii* Hance Enhances Cadmium Tolerance by Regulating ROS-Scavenger Activities and Heat Shock Proteins Expression. *Front. Plant Sci.* **2020**, *11*, 00142.
115. Charagh, S.; Hui, S.Z.; Wang, J.X.; Raza, A.; Zhou, L.; Xu, B.; Zhang, Y.Y.; Sheng, Z.H.; Tang, S.Q.; Hu, S.K.; et al. Unveiling Innovative Approaches to Mitigate Metals/Metalloids Toxicity for Sustainable Agriculture. *Physiol. Plant.* **2024**, *176*, e14226.
116. Tang, L.; Dong, J.Y.; Qu, M.M.; Lv, Q.M.; Zhang, L.P.; Peng, C.; Hu, Y.Y.; Li, Y.K.; Ji, Z.Y.; Mao, B.G.; et al. Knockout of OsNRAMP5 enhances rice tolerance to cadmium toxicity in response to varying external cadmium concentrations via distinct mechanisms. *Sci. Total Environ.* **2022**, *832*, 155006.
117. Uruguchi, S.; Kamiya, T.; Sakamoto, T.; Kasai, K.; Sato, Y.; Nagamura, Y.; Yoshida, A.; Kyojuka, J.; Ishikawa, S.; Fujiwara, T. Low-affinity cation transporter (OsLCT1) regulates cadmium transport into rice grains. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 20959–20964.
118. Luo, J.S.; Huang, J.; Zeng, D.L.; Peng, J.S.; Zhang, G.B.; Ma, H.L.; Guan, Y.; Yi, H.Y.; Fu, Y.L.; Han, B.; et al. A defensin-like protein drives cadmium efflux and allocation in rice. *Nat. Commun.* **2018**, *9*, 645.
119. Shangguan, X.; Tian, Z.; Wang, Y.; Xiao, T.; Yu, X.; Jing, W.; Peng, K.; Shen, Z.; Hu, Z.; Xia, Y. Transcription factor OsWRKY72 is involved in Cu/Cd toxicity by regulating lignin synthesis in rice. *Crop J.* **2024**, *12*, 1471–1482.
120. Ding, Y.; Gong, S.; Wang, Y.; Wang, F.; Bao, H.; Sun, J.; Cai, C.; Yi, K.; Chen, Z.; Zhu, C. MicroRNA166 Modulates Cadmium Tolerance and Accumulation in Rice. *Plant Physiol.* **2018**, *177*, 1691–1703.
121. Tan, J.; Zhang, L.; Liu, C.; Hong, Z.; Wu, X.; Zhang, Y.; Fahad, M.; Shen, Y.; Bian, J.; He, H.; et al. UCL23 hierarchically regulated by WRKY51-miR528 mediates cadmium uptake, tolerance, and accumulation in rice. *Cell Rep.* **2025**, *44*, 1153.
122. Liu, F.; Xi, M.W.; Liu, T.; Wu, X.Y.; Ju, L.Y.; Wang, D.J. The central role of transcription factors in bridging biotic and abiotic stress responses for plants' resilience. *New Crops* **2024**, *1*, 100005.

123. Bang, S.W.; Choi, S.; Jin, X.; Jung, S.E.; Choi, J.W.; Seo, J.S.; Kim, J.K. Transcriptional activation of rice CINNAMOYL-CoA REDUCTASE 10 by OsNAC5, contributes to drought tolerance by modulating lignin accumulation in roots. *Plant Biotechnol. J.* **2022**, *20*, 736–747.
124. Ao, C.W.; Xiang, G.J.; Wu, Y.F.; Wen, Y.; Zhu, Z.L.; Sheng, F.; Du, X. OsNAC15 regulates drought and salt tolerance in rice. *Physiol. Mol. Biol. Plants.* **2024**, *30*, 1909–1919.
125. Yan, Y.F.; Chou, D.H.; Kim, D.S.; Lee, B.W. Genotypic variation of cadmium accumulation and distribution in rice. *J. Crop Sci. Biotechnol.* **2010**, *13*, 69–73.
126. Feng, K.; Li, J.; Yang, Y.; Li, Z.; Wu, W. Cadmium absorption in various genotypes of Rice under Cadmium Stress. *Int. J. Mol. Sci.* **2023**, *24*, 8019.
127. Yu, Y.; Alesskh, S.; Zhu, Z.; Zhou, K.; Fernie, A.R. Multiomics and biotechnologies for understanding and influencing cadmium accumulation and stress response in plants. *Plant Biotechnol. J.* **2024**, *22*, 2641–2659.
128. Liu, M.; Huang, Z.; Xie, K.; Guo, C.; Wang, Y.; Wang, X. Mitostasis is the central biological hub underlying the response of plants to cadmium stress. *J. Hazard. Mater.* **2023**, *441*, 129930.
129. Kuang, L.; Yan, T.; Gao, F.; Tang, W.; Wu, D. Multi-omics analysis reveals differential molecular responses to cadmium toxicity in rice root tip and mature zone. *J. Hazard. Mater.* **2024**, *462*, 132758.
130. Zhu, S.; Sun, S.; Zhao, W.; Yang, X.; Chen, Z.; Mao, H.; Sheng, L. Comprehensive physiology and proteomics analysis revealed the resistance mechanism of rice (*Oryza sativa* L.) to cadmium stress. *Ecotoxicol. Environ. Safe.* **2024**, *278*, 116413.
131. Tan, J.; Fahad, M.; Zhang, L.; Wu, L.; Wu, X. Microrchidia OsmORC6 positively regulates Cadmium tolerance and uptake by mediating DNA methylation in Rice. *Rice* **2025**, *18*, 25.
132. Yue, E.; Rong, F.; Liu, Z.; Ruan, S.; Lu, T.; Qian, H. Cadmium induced a non-coding RNA microRNA535 mediates Cd accumulation in rice. *J. Environ. Sci.* **2023**, *130*, 149–162.
133. Lu, L.; Chen, X.; Chen, J.; Zhang, Z.; Zhang, Z.; Sun, Y.; Wang, Y.; Xie, S.; Ma, Y.; Song, Y.; et al. MicroRNA-encoded regulatory peptides modulate cadmium tolerance and accumulation in rice. *Plant Cell Environ.* **2024**, *47*, 1452–1470.
134. Feng, Z.; Wang, X.; Luo, Z.; Liu, A.; Wen, C.; Ma, Q.; Liu, W.; Li, X.; Ma, L.; Li, Y.; et al. Identification and expression analysis of lncRNAs in rice roots (*Oryza sativa* L.) under elevated CO₂ concentration and/or cadmium stress. *Genomics* **2025**, *117*, 110980.
135. Shao, J.F.; Xia, J.X.; Yamaji, N.; Shen, R.F.; Ma, J.F. Effective reduction of cadmium accumulation in rice grain by expressing OsHMA3 under the control of the OsHMA2 promote. *J. Exp. Bot.* **2018**, *69*, 2743–2752.
136. Jiang, S.; Li, H.; Zhang, L.; Mu, W.; Zhang, Y.; Chen, T.; Wu, J.; Tang, H.; Zheng, S.; Liu, Y.; et al. Generic Diagramming Platform (GDP): A comprehensive database of high-quality biomedical graphics. *Nucleic Acids Res.* **2024**, *53*, D1670–D1676. <https://doi.org/10.1093/nar/gkae973>.

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.