



Understanding the physiological and molecular mechanisms of grain cadmium accumulation conduces to produce low cadmium grain crops: a review

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Abstract

Soil cadmium (Cd), which can occur naturally in the environment or arise from industrial pollution, seriously affects crop quality and threatens human health. Therefore, reducing grain Cd accumulation (GCA) has become an important topic worldwide. To comprehensively assess the research status of GCA, we reviewed the research into physiological and molecular mechanisms of GCA, including the characteristics of Cd uptake, transport, and accumulation from roots to grain; furthermore, literature on GCA-related quantitative trait locus identification and gene functional analysis were reviewed. Based on physiological and molecular mechanisms, two strategies to reduce GCA, namely soil management and genetic improvement, were also critically summarized. It became clear that further research is necessary into the physiological mechanisms of Cd uptake, transportation, and accumulation in grain. It is also important to accelerate the discovery and use of effective functional markers and genes associated with low Cd accumulation and to improve the feasibility and potential value of breeding low Cd grain crops.

Keywords Grain cd accumulation (GCA) · Physiological mechanisms · Molecular mechanisms · Soil management · Genetic improvement

Introduction

Due to the rapid advancement of mining, industrial, and agricultural activities, the severity of soil pollution caused by heavy metals has escalated significantly. This problem arises from various sources, including the discharge of industrial waste water and gas, sewage irrigation, and improper use of chemical fertilizers and pesticides (Yan et al. 2021). In China, approximately 16.1% of the nation's agricultural

land surpasses the safety threshold for soil heavy metal concentration. The primary inorganic pollutants contributing to this alarming statistic are cadmium (Cd), nickel (Ni), and arsenic (As), with 7.0%, 4.8%, and 2.7% of soils exceeding the threshold, respectively (Liu et al. 2016a). Moreover, there is a concerning trend for soil plough layer in China to experience Cd-induced pollution, with its rate for increase averaged as 0.004 mg kg⁻¹ per year, which may be mainly caused by industrial waste discharge and extensive fertilizer usage (Hu et al. 2016). The rate of soil pollution increase in China far surpasses that observed in Europe (Luo et al. 2009). Accumulation of excessive Cd in crops induced by pollution has given rise to health issues, notably with the emergence of “Cd rice” and “Cd wheat”, prompting widespread concern about the impact on public health.

Cd acts as a nonessential component for both plants and animals, yet it can seriously threaten human health when accumulated in high concentrations using food chain (Dias et al. 2013; Li et al. 2019). Functioning as a plant abiotic stress contaminant, Cd exhibits troublesome characteristics, such as a low soil-adsorption coefficient, a high soil-plant

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mobility, and a substantial plant accumulation factor (Shahid et al. 2017; Chen et al. 2018). In plants, Cd exerts a role of disrupting some normal metabolisms (Fan et al. 2011; Jaouani et al. 2018), impacting crucial processes like photosynthesis and respiration (Song et al. 2019). This disruption extends to reduced root activity, slowed seedling growth, and the manifestation of small and yellow leaves, ultimately culminating in plant death (Ahmad et al. 2015; Zhang et al. 2021a). Importantly, human exposure to Cd prevalingly occurs via ingesting the plant material contaminated with cadmium, constituting a health threat even at low concentrations. Prolonged Cd exposure has been linked to a higher incidence of lung, prostate, testicular, and kidney cancers (Unsal et al. 2020; Reyes-Hinojosa et al. 2019). Consequently, extensive research efforts are underway globally to develop strategies for controlling grain Cd accumulation (GCA) in crops.

Currently, in most regions globally, the concentration of Cd in grain typically aligns with safety standards, albeit with regional variations. According to relevant criteria for food safety stipulated by the European Union (EU) and China, maximum allowable Cd concentration in rice is set at 0.2 mg kg^{-1} , while the Codex Alimentations Commission specifies a limit of 0.4 mg kg^{-1} (Yang et al. 2019a). Recent global research indicates that the average GCA concentration is 0.093 mg kg^{-1} , with a 16-fold variation in mean values among regions. Notably, South China exhibits the highest concentration at 0.32 mg kg^{-1} , followed by Argentina (0.15 mg kg^{-1}) \approx Germany (0.13 mg kg^{-1}) $>$ Japan (0.11 mg kg^{-1}) $>$ United States (0.064 mg kg^{-1}) $>$ Central-North China ($0.020\text{--}0.60 \text{ mg kg}^{-1}$) \geq Iran (0.042 mg kg^{-1}) $>$ Brazil (0.023 mg kg^{-1}) \approx South Korea (0.020 mg kg^{-1}) (Zhang et al. 2021b). However, some studies present contrasting findings, emphasizing concerns about Cd levels exceeding allowable limits. For instance, in West Bengal, a study reported GCA concentrations in rice (between the value being below the threshold to 0.49 mg kg^{-1}) and in soil samples (1.76 mg kg^{-1} to 13.8 mg kg^{-1}), surpassing the permissible limits (Majumdar et al. 2020). In Germany, an investigation into Cd uptake involving 602 soybean accessions revealed that the average Cd content should be 0.13 mg kg^{-1} , which was 12.5% higher in contrast to the stipulated threshold in EU (Franzaring et al. 2019). Additionally, in New Zealand, an investigation into the GCA content of 12 wheat varieties collected in various regions showed Cd concentrations can be $0.004\text{--}0.205 \text{ mg kg}^{-1}$, which is averaged as 0.066 mg kg^{-1} , and 7% of the varieties surpassing 0.1 mg kg^{-1} (Gray et al. 2019).

Consequently, addressing the avoidance and mitigation of soil pollution induced by heavy metal in cropland to guarantee the generation and supply of safe food has emerged as a crucial global concern. This review centers

on examining the physiological and molecular mechanisms underlying GCA and explores strategies to produce grain crops with low Cd (LCd). The review also highlights the knowledge gaps in basic research at both physiological and molecular levels which require further studies. Ultimately, it advocates for research into crop breeding with LCd, offering a theoretical foundation for producing safe and uncontaminated food.

Physiological mechanisms of GCA

With specific concentration, Cd accumulated in the soil can seriously impact plant metabolism, photosynthesis, respiration, transport, and overall growth (Sandalio et al. 2001; Zhang et al. 2014). Furthermore, it causes GCA, ultimately diminishing both crop yield and quality. The intricate physiological processes involved in GCA in crops have been investigated many times. Figure 1 illustrates the Cd uptake, transport, and accumulation, using rice as an example.

Cd uptake and transport in roots

Generally, available soil Cd is passively or actively absorbed into plant root systems through the symplast pathway. Subsequently, it undergoes transportation to aerial parts of a plant using xylem, facilitated by transpiration, and accumulates in grains via internode phloem (Feng et al. 2018; Liu et al. 2021; Uraguchi et al. 2009). Transporters associated with essential elements involve in mediation of Cd transport in plants, like Zn, Ca, Fe, and Mn. Processes such as Cd uptake and xylem loading in roots, Cd remobilization from leaf blades, and intervascular transfer in nodes play pivotal roles in redirecting Cd transport to the grain, a critical aspect of GCA (Uraguchi and Fujiwara 2013). The root cell wall acts as initial barrier in avoiding entrance of Cd to the stem. However, cell walls, composed of proteins, polysaccharides, lignin, and other phenolic compounds, also serve as a target for heavy metals. Functional groups within cell walls can form covalent or non-covalent bonds with Cd (Parrotta et al. 2015), potentially diminishing the Cd uptake by the roots.

Upon entering cells in plant root, some Cd is encapsulated within vacuoles as a complex with Cd-phytochelatin proteins (Miyadate et al. 2011), whereas the remaining Cd is conveyed to xylem. Sequestering Cd into vacuoles is acknowledged to be efficient for Cd tolerance, contributing to a reduction of Cd transport to the grain (Gao et al. 2016; Xin et al. 2018). Phytochelatins accumulate in plants when exposed to heavy metal ions, forming complexes that minimize the free Cd content in the cytosol (Grill et al. 1987). These Cd-phytochelatin complexes hinder Cd transport by binding Cd ions through metal chelation with organic acids

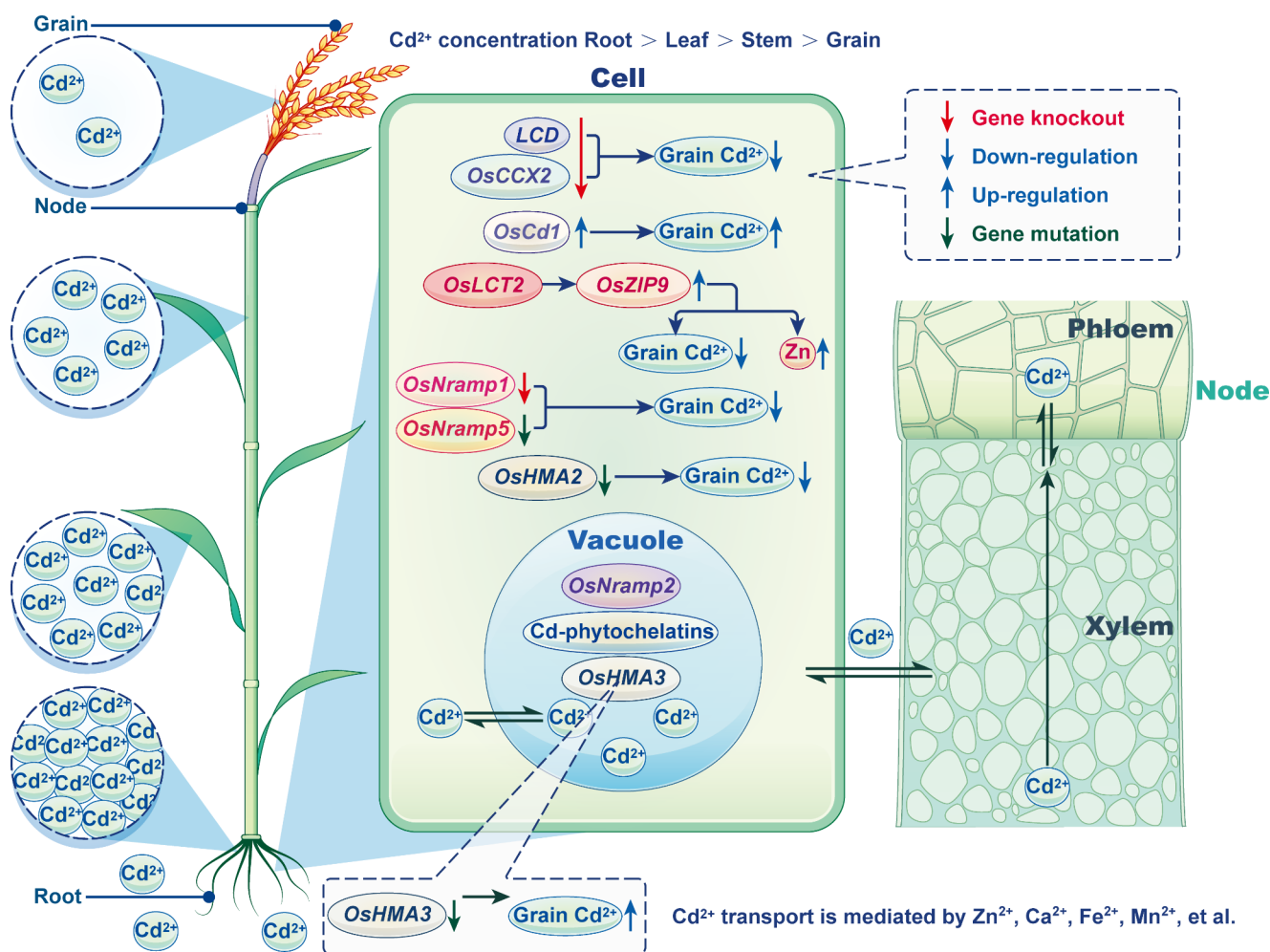


Fig. 1 Uptake, transport, and Cd accumulation in the rice plant. This figure shows that Cd is taken-up from the soil by roots and then partly chelated, accumulates in vacuoles, and partly accumulates in grain via

transport through the xylem and phloem. It also shows the localization of genes related to the regulation of Cd accumulation in root cells, which ultimately affect GCA.

in plants (Saraswat and Rai 2011). For examples, organic acids like malonic and malic acids restrict the Cd flow by forming strong bonds with Cd ions through metal chelation (Osmolovskaya et al. 2018). A one-unit increase in content of malonic and malic acids facilitates the chelation of 5.60 and 2.03 units of Cd in plants (Kocaman 2023). Research indicates that root vacuoles in maize genotypes containing high Cd (HCd) experience more severe damage compared to those in maize genotypes with LCd, which remain largely unaffected. The latter is better equipped to generate Cd chelates and sequester more Cd into vacuoles (Lin et al. 2022). Cd chelation or retention in vacuoles impedes Cd transport from roots to aboveground parts, thereby diminishing GCA.

Cd transport to and accumulation in grain

Cd loading into the grain occurs through phloem-mediated redistribution following the initial transport using the xylem

(Vanderschueren et al. 2023; Zhong et al. 2023). In durum wheat, excessive GCA did not exhibit a correlation with seedling root uptake rates or root-to-shoot translocation. Instead, it appears to be linked with Cd transport modulated by phloem to the grain (Hart et al. 1998). However, GCA in rice demonstrated independence from both the root uptake period and the Cd content in soil. While, a strong positive association was observed with the Cd content in xylem. Cd translocation from the root to the shoot via the xylem primarily affects the GCA concentration in rice (Uraguchi et al. 2009). Tanaka et al. (2007) investigated the involvement of rice phloem to Cd transport to the grain and unveiled that 91–100% of the Cd was derived from the topmost internode of rice plants during grain-filling.

When the plants are under reproductive growth, they absorb Cd through their roots and transport it to grain through stems and leaves. In wheat, the early filling stage is deemed as a critical period for transporting accumulated

Cd from leaves to the grain (Ma et al. 2022). Nodes serve as core organs responsible for transferring Cd from xylem to phloem, crucially contributing to the Cd accumulation from soil to grain during filling (Harris and Taylor 2013; Zhong et al. 2023). Research conducted by Liu et al. (2021) revealed a positive relationship between GCA in brown rice and that in the upper nodes, along with the efficiency of Cd translocation from roots to nodes. Shi et al. (2019) studied the spatial arrangement and evolving dynamics of Cd concentration in one HCd and one LCd common wheat cultivar. The outcomes indicated substantial differences in GCA concentrations between the two cultivars, while the concentrations in rachis and glumes remained similar. This signifies that the two cultivars exhibit distinct regulatory mechanisms with respect to Cd retransfer and redistribution from rachis and glumes to grain during the reproductive stage.

Molecular mechanisms of GCA

Plant genes exert control over physiological and metabolic responses to Cd stress by managing the production of their specific proteins and functionally related proteins through transcription factors. In the last four decades, the accelerated progress in technologies associated with molecular marker and high-throughput sequencing platforms has advanced

the exploration of quantitative trait loci (QTLs) and genes. Identifying QTLs and genes linked to GCA have attracted increasing attention and has garnered escalating interest, emerging as a crucial research domain for pinpointing LCd grain germplasm in molecular breeding programs.

QTL identification for GCA

Linkage mapping (LM) and association mapping (AM) are two essential methods for identifying quantitative trait loci (QTLs), based on the construction of genetic maps from biparental segregation populations and the linkage disequilibrium of natural populations, respectively. While numerous QTLs associated with Cd uptake, transport, and accumulation in crops have been extensively delved into, there is a notable scarcity of reports on QTLs directly controlling GCA. Consequently, only those QTLs directly related to GCA in some common crops like rice (Ishikawa et al. 2005, 2010; Sato et al. 2011; Guo et al. 2019; Wang et al. 2020; Zhang et al. 2018; Zhao et al., 2018; Liu et al. 2019b; Pan et al. 2020), wheat (Knox et al. 2009; Oladzaad-Abbasabadi et al. 2018; Ban et al. 2020), soybean (Jegadeesan et al. 2010; Benitez et al. 2010), barley (Wu et al. 2015), and maize (Tang et al. 2021a), are detailed in Table 1. For instance, in rice, 14 QTLs for GCA, with the phenotypic variation explained (PVE) of 2.40–4.82%, were identified

Table 1 Quantitative trait locus identification related to GCA

Crop	Method	Population	QTL Number	Chromosome	PVE (%)	Reference
Rice	LM	CSSL	3	C3, C6, C8		Ishikawa et al. 2005
	LM	BIL	2	C2, C7	11.80, 35.50	Ishikawa et al. 2010
	LM	RIL	2	C3, C11	13.86/8.29, 9.41/12.91	Sato et al. 2011
	LM	F ₂	2	C9, C12	4.92, 5.18	Guo et al. 2019
	LM	RIL	5	C7, C8, C9	5.09–10.53	Wang et al. 2020
	AM	Natural population	62	C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12		Zhang et al. 2018
	AM	Natural population	14	C1, C2, C3, C4, C7, C8, C11	2.40–4.82	Zhao et al. 2018
	AM	Natural population	17	C1, C2, C3, C4, C6, C7, C8, C9, C10, C11, C12		Liu et al. 2019b
	AM	Natural population	35	C1, C2, C3, C4, C6, C7, C8, C9, C10, C11, C12		Pan et al. 2020
	Wheat	LM	DH	1	C5B	> 80
LM		RIL	1	C5B	70.6	Oladzaad-Abbasabadi et al. 2018
LM		DH	2	C4B, C6B	9.4–25.4, 9.0–17.8	Ban et al. 2020
Soybean	LM	RIL	1	C9	57.3	Jegadeesan et al. 2010
	LM	RIL, NIL	1	C9	82.4/56.7/74.9	Benitez et al. 2010
Barley	AM	Natural population	15	C2H, C3H, C4H, C5H, C7H	2.9–12.6, 3.3–11.3	Wu et al. 2015
Maize	AM	Natural population	2	C2	20.03, 23.78	Tang et al. 2021a

LM - linkage mapping; AM - association mapping; CSSL - chromosome segment substitution line; BIL - backcross inbred line; RIL - recombinant inbred line; DH - doubled haploid; NIL - near isogenic line; PVE - phenotypic variation explained

on seven chromosomes based on an AM natural population containing 312 rice accessions (Zhao et al. 2018). Another example is in soybean, where a significant QTL for grains with LCd, located on chromosome 9, explained 57.3% of the phenotypic variation, which were derived from constructing an RIL population using HCd and LCd parents (Jegadeesan et al. 2010).

A comprehensive review of previous studies revealed the recurrent detection of certain QTLs for GCA were repeatedly detected across diverse populations, generations, environments, and mapping methods. In rice, QTL *qGCd7*, demonstrating a significant PVE for GCA of 35.5%, was identified in a recombinant inbred line (RIL) population and consistently confirmed in chromosome segment substitution lines (CSSLs), F_2 , and germplasm populations (Ishikawa et al. 2010; Zhang et al. 2018). Another rice QTL, *qLCdG11*, with an average PVE for GCA of 11.16% (9.41% and 12.91%), was repeatedly detected across two generations (Sato et al. 2011). In wheat, the QTL *QCdu.spa-B1*, exhibiting an average PVE for GCA of 80%, was consistently detected in 2 years of testing (Knox et al. 2009). Two additional wheat QTLs, namely *QCdc.4B-kita* and *QCdc.6B-kita*, with PVE values for GCA ranging from 9.4 to 25.4% (chromosome 4B) and 9.0–17.8% (6B), respectively, were recurrently detected over 3 years (Ban et al. 2020). In soybean, the QTL *Cda1*, boasting a PVE of 57.3%, was consistently identified in 2 years and was further validated in different populations (Jegadeesan et al. 2010). Another soybean QTL *Cd1*, with the average PVE of 71.3% (82.4%, 56.7%, and 74.9%), was repeatedly detected in three RIL generations and a NIL population. In barley, the two main QTLs, which were *8586–1221* and *ConsensusGBS0086-5*, explaining 12.6%/11.3% and 9.5%/8.5% of the average PVE, respectively, were repeatedly detected in two environments (Wu et al. 2015). In maize, the QTL *qCd1*, featuring a PVE of 20.03%, was consistently detected across four different environments and was further validated through AM and bulked segregant RNA-seq analyses (Tang et al. 2021a). The above major-effect QTLs exhibit high reliability and hold potential for utilization in marker-assisted selection (MAS) to reduce grain Cd concentration.

Cloning and functional analysis of genes associated with GCA

Growth of crop varieties with LCd accumulation hinges on identifying genes linked to reduced Cd content, necessitating a deeper investigation into Cd uptake and transport mechanisms (Chen and Wu 2020). Studies on genotypes, including mutants with varying Cd accumulation levels, have necessitated the identification of Cd transporter proteins in rice and other grain crops. Numerous genes participated in

regulating Cd accumulation were uncovered (Fig. 1), like the heavy metal ATPase (*HMA*) (Takahashi et al. 2012), the *Natural resistance-associated macrophage protein* (*Nramp*) (Takahashi et al. 2011), the Zn/Fe-regulated transporter-like (*ZIP*) (Guerinot 2000; Zheng et al. 2018), and the low-affinity cation transporter (*LCT*) (Uraguchi et al. 2011). In our previous investigation, the transcriptomic response was compared at different Cd concentrations in a HCd and a LCd sunflower cultivar, and several Cd-related candidate genes were identified, namely *ATP-binding cassette* (*ABC*), *ZIP*, *heavy metal-associated isoprenylated plant protein* (*HIPP*), *Nramp*, and *HMA* (Fu et al. 2022). These candidate genes, crucial for understanding Cd response mechanisms, necessitate further functional verification. Notably, significant strides have been taken in unraveling genes correlated with Cd uptake, transport, and accumulation in grains, thereby influencing GCA (Table 2).

OsHMA2 primarily conveys Zn and Cd and is discovered in root pericycle and phloem of diffuse vascular bundles in the nodes (Yamaji et al. 2013). A reduction in function or downshift of *OsHMA2* expression has been demonstrated to lower Cd content in grains (Satoh-Nagasawa et al. 2012). *OsHMA3*, a paralogous gene of *OsHMA2* in root cell vacuoles, facilitates high root-to-shoot Cd translocation rates (Miyadate et al. 2011). It acts by restricting Cd translocation from roots to aboveground tissues, selectively sequestering Cd into root vacuoles (Miyadate et al. 2011; Ueno et al. 2010). Liu et al. (2020b) highlighted the significance of sequence variation in the *OsHMA3* promoter *GCC7* in regulating variations in Cd accumulation between *indica* and *japonica* rice accessions. The HCd and LCd accumulation alleles, *GCC793-11* and *GCC7PA64s*, exhibit distinct *OsHMA3* initiation activities, leading to varying GCA contents between the two subspecies. Genotypes with knockdown mutant alleles of *OsHMA3* show reduced the capability to isolate Cd in vacuoles, causing HCd in shoots and grains (Sui et al. 2019; Yan et al. 2016; Zhao and Wang 2020). The *OsHMA3* expression exposed to *OsHMA2* promoter increased Cd storage in vacuoles from various parts, greatly lowering GCA in rice (Shao et al., 2018). Tang et al. (2021a) reported a potential gene (i.e., *ZmHMA3*) capable of influencing GCA in maize. By capitalizing on the inherent sequence variations in *ZmHMA3* among a diverse array of maize lines, four PCR-based molecular markers were formed, effectively discerning five haplotypes.

OsNramp5, expressed in roots, is crucial in Cd uptake and transport. Mutations in it remarkably weaken the Cd uptake by roots, diminishing GCA content in rice (Ishikawa et al. 2012). Through CRISPR-Cas9 gene-editing system, a novel *indica* cultivar with LCd accumulation was developed following the knockout of *OsNramp5*. The mutant consistently maintained a GCA content below 0.05 mg kg^{-1}

Table 2 Cloning and functional analysis of genes related to GCA

Gene family	Gene name	Probable function	References
<i>HMA</i>	<i>OsHMA2</i>	Cd transport	Yamaji et al. 2013; Satoh-Nagasawa et al. 2012
	<i>OsHMA3</i>	Cd root-to-shoot translocation	Miyadate et al. 2011; Ueno et al. 2010; Liu et al. 2020b; Sui et al. 2019; Yan et al. 2016; Zhao and Wang 2020; Shao et al. 2018
	<i>ZmHMA3</i>	Cd root-to-shoot translocation	Tang et al. 2021a
<i>Nramp</i>	<i>OsNramp5</i>	Cd uptake, transport	Ishikawa et al. 2012; Tang et al. 2017
	<i>OsNramp1</i>	Cd uptake, transport	Chang et al. 2020
	<i>OsNramp2</i>	Cd transport	Zhao et al. 2018
<i>ZIP</i>	<i>OsZIP1</i>	Cd transport	Liu et al. 2019a
	<i>OsZIP3</i>	Cd transport	Tian et al. 2019
	<i>OsZIP7</i>	Cd transport	Tan et al. 2019
	<i>HvZIP3, HvZIP8</i>	Cd transport	Sun et al. 2015
<i>LCD</i>	<i>OsLCD</i>	Cd transport	Shimo et al. 2011
<i>CCX</i>	<i>OsCCX2</i>	Cd efflux transport, loading of Cd into xylem vessels	Hao et al. 2018; Guo et al. 2020
<i>LCT</i>	<i>OsLCT1</i>	Transport of Cd into grain	Shimpei et al. 2014; Uraguchi et al. 2011
	<i>OsLCT2</i>	Transport of Cd into grain	Tang et al. 2021b
<i>MFS</i>	<i>OsCd1</i>	Cd uptake and accumulation	Yan et al. 2019

HMA - heavy metal ATPase; *Nramp* - natural resistance-associated macrophage protein; *ZIP* - zinc/iron-regulated transporter-like protein; *LCD* - low Cd; *CCX* - cation/Ca exchanger; *LCT* - low affinity cation transporter; *MFS* - major facilitator superfamily

and demonstrated unaffected yields when cultivated in a Cd-contaminated paddy field, in contrast to the same cultivar grown in uncontaminated soil (Tang et al. 2017). *OsNramp1* predominantly expresses on plasma membrane of root cells, excluding central vascular tissues and mesophyll cells. Knockdown of *OsNramp1* results in a reduction in Cd accumulation, although its impact is less pronounced than that of *OsNramp5*. Declined Cd content is more substantial in double mutants of *OsNramp1* and *OsNramp5* in comparison to either single mutant. Another gene within this family, *OsNramp2*, expressed in vacuoles, likely encodes a functional Cd transporter (Zhao et al., 2018). The combination of *OsNramp1*, *OsNramp5*, and *OsHMA3* has been employed in breeding the *indica* rice variety 93–11 with low GCA (Wang et al. 2021).

ZIP can transport various cations, like Zn, Fe, Mn, and Cd. *OsZIP1*, identified as a metal-detoxifying transporter, is crucial to avoid too much Zn, Cu, and Cd are deposited in rice (Liu et al. 2019a). *OsLCT1*-*OsHMA2*-*OsZIP3* co-expression effectively diminishes the Cd translocation and accumulation, mitigate oxidative stress triggered by Zn and Cd, ultimately enhancing the quality of rice grain (Tian et al. 2019). *OsZIP7* exerts an active effect in loading Zn and Cd into xylem in roots and facilitating inter-vascular transfer in nodes, and its specific function involves preferentially directing Zn and Cd to developing tissues and grains (Tan et al. 2019). Through DNA microarray analysis and confirmation in RNA interference (RNAi) plants, two pivotal genes,

HvZIP3 and *HvZIP8*, have been identified as contributors to low GCA in barley (Sun et al. 2015).

The *LCD* protein predominantly localizes to the cytoplasm and nucleus, with gene expression occurring in vascular tissues of the roots and cells associated with phloem in leaves. In the Cd-tolerant *lcd* knockout mutant, the GCA level in rice decreased by approximately 50%, in contrast to the wild type. Importantly, no considerable variation was observed in plant biomass or grain yield between the *lcd* knockout mutant and the wild type (Shimo et al. 2011).

The gene responsible for cation/Ca exchange, specifically *OsCCX2*, facilitates the direct transport of Cd from the roots to the grain. The knockout mutant of the *OsCCX2* gene led to a notable decrease in Cd content within the grain (Hao et al. 2018). Guo et al. (2020) focusing on Cd distribution in rice cultivar ‘YaHui2816’ exhibited a cultivar with a LCd concentration in grain and HCd concentration in straw. This finding signified that *OsHMA2*, *OsCCX2*, and *OsZIP7* involved in Cd retention at node II. Consequently, this restrains transporting Cd to the grain.

A rice Cd transporter, *OsLCT1*, functions at the nodes, where Cd is transported to the grain. The regulation of *OsLCT1* has been demonstrated to yield “LCd rice” without influencing agronomic traits. In the model *indica* cultivar ‘Kasalath’, *OsLCT1* was observed to be highly expression in the reproductive stage than in the vegetative stage (Uraguchi et al. 2014). Conversely, *OsLCT2* increased the Zn concentrations in roots under an overexpression condition by up-regulating *OsZIP9*, which reduced GCA by limiting

Cd enter the xylem and restraining root-to-shoot Cd translocation in rice (Tang et al. 2021b).

OsCdl exerts a role in Cd uptake by rice roots and facilitates GCA in rice. The inherent variation observed in *OsCdl*, characterized by a missense mutation Val449Asp, is accountable for the disparity GCA between the *indica* and *japonica* subspecies of rice (Yan et al. 2019).

Strategies to produce LCd grain crops

Enhancing our comprehension of the physiological and molecular mechanisms of GCA can pave the way to produce grain crops with LCd, facilitating the translation from laboratory research to practical field applications. Two strategies have been proposed: soil management and genetic improvement. Soil management endeavors to diminish the effective Cd content in the soil through physical, chemical, or biological methods. This strategy aims to enhance the physiological and metabolic environment in plants as well as modulate Cd absorption, transport, and metabolism in grain crops. On the other hand, genetic improvement focuses on identifying valuable QTLs or alleles associated with LCd. It aims to establish efficient breeding technologies that integrate conventional breeding, molecular marker-assisted breeding, gene editing, and other modern biotechnological approaches, and finally cultivate crop varieties containing LCd.

Soil management

Appropriate utilization of conventional agronomic methods on farmland polluted by Cd has demonstrated the potential to yield crops that meet relevant national stipulations on limiting the Cd content (Kang et al. 2020; Li et al. 2017; Liu et al. 2016b). Effective soil management, encompassing precise control of soil moisture and nutrient levels, along with the regulation of soil pH and redox potential, empowers farmers to curtail Cd migration from soil to roots, thereby contributing to a reduction in GCA (Hussain et al. 2021; Yuan et al. 2020). Strategic control of water and fertilizer is conducive for weakening the utilization of heavy metals in paddy soils. Specifically, flooding is a method to decrease GCA in rice, with additional benefits observed when lime is concurrently applied (Han et al. 2018). However, it's worth noting that flooding may lead to increased arsenic accumulation in crops (Hu et al. 2013). Notably, the implementation of film mulch technology, as demonstrated by Wang et al. (2015), exhibited a 50% reduction in GCA in rice when comparing to the control. Under the condition of collective use of complementary measures (like biochar and silica foliar fertilizer), the reduction in GCA content is enhanced.

Current research is actively exploring effects of various factors, individually or jointly, in controlling Cd contamination in plant tissues a (Tang et al. 2020). While these investigations offer valuable insights, a more systematic approach is required, necessitating further comprehensive research in this domain.

Applying fertilizers and soil conditioners judiciously can enhance the physical and chemical properties of soil, diminish plant Cd uptake from soil, and foster plant growth. The extent of GCA is intricately linked to Cd bioavailability in soil. Within a specific range of soil pH values, soil acidification has been identified as a factor that amplifies the available Cd content in the soil, subsequently elevating GCA (Chen et al. 2021). Conversely, alkaline soil amendments can form Cd complexes, chelates, and precipitates, effectively weakening the bioavailability of soil Cd (Hamid et al. 2019; Jin et al. 2020). Huang et al. (2020) applied quicklime for 4 consecutive years to manage soil acidity in Cd-polluted farm soils. The outcomes revealed an average increase in soil pH by 0.57, a 17% reduction in interchangeable or water-soluble Cd components in soil, a 10% increase in organic binding of Cd components, and a decline in GCA concentration in crops below the threshold (0.2 mg kg^{-1}). Various physical and biochemical soil amendments, like engineered nanoparticles (Fox et al. 2020), salicylic acid (Li et al. 2019; Majumdar et al. 2020), and melatonin (Lv et al. 2019), have been employed to mitigate plant Cd uptake. Sarwar et al. (2015) demonstrated that spraying a ZnSO_4 solution at a specific concentration onto wheat leaves during the booting completes with Cd uptake, effectively reducing the GCA in wheat and crops grown on soil suffering from Cd pollution.

Isolating and identifying Cd-tolerant microorganisms from soil suffering from Cd pollution and exploring the potential of plant-microbial symbiosis for Cd remediation offer promising avenues for soil bioremediation and mitigating GCA (Abbas et al. 2020). Wang et al. (2019) demonstrated that treating soil suffering from Cd pollution the fermentation broth of *Bacillus cereus* strain M4 could enhance the growth of pot-grown rice seedlings in soil after Cd pollution, resulting in a decrease in the GCA in rice from 0.309 to 0.186 mg kg^{-1} . Arbuscular mycorrhizal fungi, which naturally colonize in plant roots, contribute to its growth and is key in conferring tolerance to heavy metals (Garg and Bhandari 2014). *Pseudomonas taiwanensis* WRS8 associated with wheat has been shown to reduce Cd uptake. This is achieved by enhancing the adsorption of Cd on the root surface suppressing the expression of genes linked to Cd uptake and transport in wheat. In contrast to the controls, there was a substantial reduction in Cd levels in both roots (78–85%) and above-ground tissues (88–94%) at days 3 and 10 after inoculation, respectively (Cheng et al.

2021). Li et al. (2020) observed that arbuscular mycorrhizal fungi reduces GCA in maize but may also have adverse effects on maize seedling growth. This highlights the need for further exploration and optimization in the selection and application of microorganisms for soil Cd remediation.

Genetic improvement

The cultivation of crops containing LCd represents a strongly effective approach for mitigating the risk of GCA in crops and safeguarding human health (Grant et al. 2008; Ishikawa 2020; Liu et al. 2020a; ZaidImdad et al. 2018). The breeding technologies employed for crops with LCd have evolved from traditional breeding approaches to a synergistic blend of traditional and molecular breeding methods. This progression signifies a shift from empirical breeding practices to more precise and design-oriented breeding strategies.

Efforts to mitigate grain GCA involve manipulating Cd transporter proteins through strategies such as overexpression or knockout of the transporter genes, and MAS breeding based on genotypic differences in GCA (Ma et al. 2021). Chen et al. (2020) employed molecular marker-assisted breeding to individually introgress the *OsHMA3* gene or the *qIGCd3* QTL, both associated with LCd accumulation, into the recipient parent rice accession ‘C5S’. The resulting improved material consistently expressed the LCd trait, with the average grain Cd concentration reduced by 52.8% or 50.8% for those carrying *OsHMA3* or *qIGCd3*, respectively, compared to wild-type ‘C5S’. Several studies highlighted negative associations between Cd uptake and the concentrations of other mineral elements when a plant grows (Hou et al. 2021; Jia et al. 2016). HCd accumulation varieties tend to over-accumulate calcium, magnesium, manganese, iron, zinc, and other mineral elements, while wheat grain of LCd varieties may be deficient in essential nutrients (Qin et al. 2021). In rice, *OsNramp5* serves as the major transporter for both Cd and manganese (Mn). Yang et al. (2019b) employed the CRISPR-Cas9 gene editing technique to knock out *OsNramp5* in two japonica rice cultivars, leading to significantly lower GCA concentrations, albeit with reduced Mn accumulation. This negatively impacted various agronomic traits, including plant height, seed setting rate, and grain number per panicle, resulting in a slight decrease in crop yield. Some LCd cultivars maintain normal concentrations of essential minerals (Luo et al. 2018), making them valuable parental materials for LCd cultivar breeding. Through conventional and molecular breeding techniques, either individually or in combination, valuable alleles, such as *lcd*, have been selected or designed and integrated into new cultivars to achieve a balance between high yield and quality with low GCA.

Conclusion and future perspectives

The comprehension of physiological regulatory mechanisms in plants exposed to Cd is advancing. However, there is a lack of systematic exploration into the physiological mechanisms governing Cd distribution and accumulation in crops. For example, the mechanisms behind LCd accumulation in the storage roots of sweet potatoes remain unclear. This includes the factors influencing why the Cd absorbed by root is accumulated primarily in the feeder roots rather than storage roots (Zhang et al. 2020). Such uncertainties may be attributed to the limitations in conditions and facilities in the research process. Many studies focusing on the physiology of regulating Cd stress during the seedling stage, but there is a relative scarcity of corresponding research at later growth stages, an important point because GCA is primarily determined during the reproductive stage.

In major crops, predecessors have identified several QTLs for GCA that exhibit stability across multiple populations, generations, environments, and mapping methods. These reliable QTLs hold potential for application in MAS. However, it's noteworthy that some QTLs for GCA are consistently localized on the same chromosomes across different studies. The absence of bridge markers necessitates further confirmation of the consistency and stability of these QTLs through the accumulation of additional data in future investigations. In conjunction with QTL identification and gene cloning efforts, seven candidate genes, namely *OsHMA3*, *OsNRAMP1*, *OsNRAMP5*, *OsLCD*, *CAL1*, *OsABC24*, and *OsCd1*, which co-located with major-effect QTLs, were identified, although this represents a limited number. Consequently, there is a need to identify and validate Cd-related functional markers or regulatory genes with practical breeding significance. At present, most studies involve only the growth or physiological metabolic responses of crops to Cd, with limited attempts to elucidate the physiological regulation routes induced by Cd-related genes in crops. Hence, it is imperative to systematically analyze the molecular foundation of physiological traits related to Cd accumulation.

The strategies aimed at reducing GCA by diminishing Cd bioavailability in the soil through physical, chemical, or biological interventions have been extensively studied and can be promptly applied in the short term to crop production systems. However, research focused on reducing grain Cd concentration in crops at the genetic level is mostly predominantly in the initial or theoretical research stage. In contrast, most of the varieties with LCd have been identified employing traditional screening methods, and there are few reports on the development of varieties with consistently stable LCd grain based on modern biotechnologies. By combining comparative grain Cd concentration evaluation and LCd allelic genotyping, Sun et al. (2022) successfully developed

a new variety with LCd (‘Lushansimiao’), which exhibited low GCA content in large-scale field trials. However, the stability of this variety requires further investigation under diverse production conditions, environments, and years. Future breeding endeavors should concentrate on integrating traditional and molecular techniques to accurately pyramid multiple valuable LCd accumulation alleles, and finally giving rise to new crop varieties characterized by high yield, excellent quality, and LCd accumulation.

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Declarations

Conflict of interest The authors declare that they have no competing interest.

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