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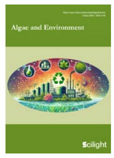

Article

Phytohormone-Mediated Responses of Microalgae to Metal Stress: From Molecular Regulation to Potential Applications in Ecological Remediation

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Abstract: Heavy metal pollution caused by industrial wastewater has posed a severe threat to water ecological security and human health. Traditional treatment technologies are limited by high costs and the risk of secondary pollution. In contrast, microalgal bioremediation technology, which features high efficiency, environmental friendliness, and potential for resource recycling, has emerged as a cutting-edge research focus. This study systematically examines the toxic response mechanisms of microalgae under heavy metal stress, including lipid peroxidation-mediated membrane damage, obstruction of the photosynthetic electron transport chain, competitive inhibition of key enzyme activities, and reactive oxygen species (ROS)-triggered oxidative stress cascades. Furthermore, the tolerance mechanisms of microalgae are thoroughly analyzed, encompassing cell wall adsorption, activation of antioxidant defense systems, regulation of metal transporters, and coordination of phytohormone signaling networks. Phytohormones mitigate heavy metal stress by modulating the expression of cell division-related genes, influencing metal transporter synthesis, enhancing membrane stability, and activating antioxidant enzymes. This study also incorporates multi-omics analyses and discusses the potential of synthetic biology approaches to engineer phytohormone metabolic pathways, with the aim of developing smart, heavy metal-responsive microalgal strains. This provides a systematic framework from fundamental mechanism analysis to applied innovation, promoting the development of microalgal bioremediation technology toward greater precision and intelligence.

Keywords: microalgae; phytohormone; heavy metal stress; bioremediation; molecular regulation

1. Introduction

Heavy metal pollution caused by industrial wastewater discharge has become a global environmental issue. Heavy metals such as Cd, Pb, Cu and other heavy metals have the characteristics of persistence, bioaccumulation and high toxicity after entering the water body through industrial activities [1]. These heavy metal ions not only persist in the environment, but also accumulate step by step through the food chain. After entering the water body, heavy metal pollution directly endangers aquatic organisms, interferes with their physiological metabolism, growth and reproduction, and leads to a sharp decline in biodiversity [2,3]. In addition, once entering the human body through drinking water or food, it will continue to accumulate in important organs such as liver and kidney, causing nervous system damage [4], organ failure [5], and even cancer [6]. At present, heavy metal pollution in industrial wastewater has posed a serious threat to ecological environment security and human health. In-depth exploration of its pollution characteristics and hazard mechanism is a key prerequisite for formulating effective governance strategies and maintaining ecological balance and public health.

The treatment of heavy metal wastewater mainly depends on chemical precipitation, ion exchange and membrane separation technology [7]. In specific scenarios, although these methods have the advantages of high removal efficiency, there are also problems such as ion exchange resin regeneration costs, resulting in high operating costs, secondary pollution, difficult disposal of chemical sludge, and inability to recover heavy metal resources [8,9]. Especially for low concentration (<10 mg/L) heavy metal wastewater, the treatment cost is high and the efficiency is generally low, so it is difficult to achieve simultaneous purification of complex systems with multi-metal coexistence [10]. In addition, traditional technologies lack the ability to biotransform pollutants, and cannot convert heavy metals into low-toxic or non-toxic forms by means of microbial redox and methylation reactions, which makes it difficult for traditional technologies to solve the problem of bioaccumulation of heavy metals in ecosystems [11].

Bioremediation technology shows greater potential in solving the problem of heavy metal bioaccumulation. Microalgae, as a natural bioremediation agent, exhibits excellent adsorption capacity for heavy metals by virtue of its good electron mobility, large specific surface area and rich functional groups (carboxyl, amino, phosphate, etc.) on the cell wall of algae [12]. Aneja et al. [13] reported that *Spirulina* sp. can adsorb a large amount of Pb^{2+} and Zn^{2+} within 15 min of initial contact with metal solution, and has a high chelation effect on Pb^{2+} and Zn^{2+} at low equilibrium concentration, which also proves that microalgae has a good adsorption effect on heavy metal ions. Moreover, the endogenous phytohormone system of microalgae establishes a multi-level defense mechanism by regulating the expression of key genes such as glutathione (GSH) synthase and metallothionein (MT). Auxin (IAA) can increase the activity of phytochelatin synthase (PCS) [14]. Cytokinins (CKs) enhances reactive oxygen species (ROS) scavenging ability by activating ascorbic acid-glutathione cycle [15], while ethylene signaling pathway regulates zinc and iron transporter protein (ZIP) transporters to achieve Cu^{2+} compartmentation [16,17]. This "adsorption-detoxification-transformation" trinity mechanism enables microalgae to have significant advantages in terms of efficiency improvement of 40-70%, cost-effectiveness reduction of 60%, and ecological safety in remediation [18].

Although the mechanism of phytohormone regulation provides a new direction for microalgae remediation technology, it still has great development prospects in molecular function [19,20]. However, the specificity of phytohormone signal transduction pathway in algae has not been elucidated, the synergistic and antagonistic effects of multiple hormones are not systematically studied, and the hormone regulation targets of transmembrane transporters are not clear [21]. Therefore, this review will construct an analytical framework of "stress perception-signal transduction-physiological response". This review analyzes the interactions between heavy metals and microalgae cells, focusing on binding mechanisms of cell wall components (polysaccharides and proteins) and the physiological roles of phytohormones in microalgal responses to heavy metal stress. We examine the molecular mechanisms underlying phytohormone-mediated stress adaptation and further explore how integrating multi-omics data with synthetic biology strategies enables the directional engineering of phytohormone metabolic pathways. These approaches facilitate the development of engineered microalgal strains with enhanced heavy metal sensing and tolerance capabilities, ultimately advancing the theoretical foundation for precision bioremediation technologies.

2. Interaction between Microalgae and Metal

2.1. Toxic Effects of Metals on Microalgae

The toxic effects of metals on microalgae depend on their species, concentrations and chemical forms, among which essential metals (e.g., Fe, Zn) and non-essential toxic metals (e.g., Cd, Pb, Hg) exhibit dual effects [22]. Low concentrations of essential metals (e.g., Fe^{2+}, Zn^{2+}) are essential for the growth of microalgae and are involved in key metabolic processes, such as Fe involved in chlorophyll synthesis, Zn-regulated enzyme activity and Fe-S protein electron transfer. However, they can still cause toxicity when excessive. For example, Fe^{3+} catalyzes the formation of oxhydryl radicals through Fenton reaction, resulting in oxidative damage [23], while high concentration of Zn^{2+} competitively inhibits the function of Mg^{2+} in photosynthesis and interferes with Photosystem II (PSII) activity [24]. The sensitivity of different algae to metal stress is also different, and the difference can reach 2–3 orders of magnitude, and this sensitivity is related to metal species and algae species characteristics [25]. For example, the EC_{50} of *Raphidocelis subcapitata* to Zn^{2+} was 0.20 mg/L. The tolerance concentrations of other algae species such as *Chlorella sorokiniana* and *Scenedesmus acuminatus* to Zn^{2+} can reach 0.6–1.0 mM [26]. This indicates that different kinds of microalgae have different tolerance to the same metal.

This difference may affect its response to plant hormone regulation. In contrast, toxic metals (Cd, Pb, Hg) can destroy the physiological functions of microalgae even at extremely low concentrations. For example, after exogenous addition of Cd and Co during the growth of *Raphidocelis subcapitata*, the IC_{50} were 0.67 µM and 1.53 µM, respectively [27]. The toxic mechanisms mainly include cell membrane damage, photosynthesis inhibition, enzyme activity interference, oxidative stress and ROS accumulation [28].

2.1.1. Membrane Damage

Cell membrane is the key barrier to maintain the homeostasis of microalgae cells. High concentrations of heavy metal ions (e.g., Cd^{2+}, Pb^{2+}, Cu^{2+}) can bind to membrane phospholipids through electrostatic interaction, destroy the hydrophobic-hydrophilic balance of lipid bilayers, reduce membrane fluidity, and induce lipid peroxidation (e.g., malondialdehyde accumulation) [29]. In addition, Cu^{2+} and other metals can produce ROS through Fenton reaction, attacking unsaturated fatty acids, resulting in membrane perforation or collapse. Membrane damage causes electrolyte leakage, loss of photosynthetic pigments and increased heavy metal influx, which aggravates oxidative stress and eventually leads to growth arrest and even cell lysis [30].

2.1.2. Photosynthesis Inhibition

Heavy metal ions (such as Cd^{2+}, Pb^{2+}, Cu^{2+}) inhibit the photosynthetic electron transport chain (PETC) by destroying the chloroplast structure and thylakoid membrane integrity. Cu^{2+} and Pb^{2+} can bind to the D1 protein of PSII and hinder the function of water splitting complex [31]. Cd^{2+} competitively binds to iron-sulfur clusters in ferredoxin and blocks electron transfer [32]. In addition, heavy metals interfere with the activity of photosynthetic-related enzymes, resulting in a decrease in adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide phosphate (NADPH) synthesis, and a decrease in photosynthetic efficiency (Fv/Fm) [33]. Low concentration stress may cause reversible inhibition, while high concentration leads to irreversible disintegration of chloroplasts [34].

2.1.3. Enzyme Activity Interference

Heavy metal ions (such as Cd^{2+}, Pb^{2+}, Cu^{2+}) can change the conformation of the enzyme or inactivate it by binding to the thiol, carboxyl or histidine residues of the enzyme active center. For example, Cd^{2+} and Pb^{2+} inhibited the activities of superoxide dismutase (SOD) and catalase (CAT), and weakened the antioxidant defense system [35]. Excessive Cu^{2+} can competitively replace Mg^{2+}, Zn^{2+} and other cofactors to interfere with the functions of photosynthetic enzymes and electron transport chains [24]. In addition, heavy metals inhibit ATPase activity, affect energy metabolism and ion transport, and ultimately lead to cell growth arrest.

2.1.4. Oxidative Stress and ROS Accumulation

Heavy metals (such as Cd^{2+}, Hg^{2+}) induce ROS accumulation directly or indirectly, breaking the redox balance. Cd^{2+} can replace the essential metal ions (such as Cu, Zn, Fe) in antioxidant enzymes, resulting in the accumulation of superoxide anion (O^{2-}) and hydrogen peroxide (H_2O_2) [36]; Hg^+ binds to the sulfhydryl group with high affinity, depleting GSH [37]. Excessive accumulation of ROS leads to lipid peroxidation, protein denaturation and deoxyribonucleic acid (DNA) damage, eventually leading to apoptosis [38]. Increased electron leakage in the electron transport chain of mitochondria and chloroplasts further exacerbates ROS production, causing irreversible damage when it exceeds the antioxidant system's scavenging capacity [39].

2.2. Tolerance Strategies of Microalgae to Metals

For example, abscisic acid (ABA) and CKs can optimize the metal bioremediation strategy of microalgae by enhancing metal absorption capacity and finely regulating hormone levels [40]. In contrast, hormones in microalgae have been shown to have a unique regulatory mechanism for metal stress response., ABA in higher plants mainly regulates seed germination and abiotic stress tolerance [41], while the mechanism of hormone-mediated metal tolerance in bacteria is less studied [42]. In terms of detoxification mechanisms, microalgae are also different from higher plants and microorganisms. Microalgae mainly detoxify through intracellular and extracellular processes [43]. In terms of detoxification mechanism, microalgae and higher plants and microorganisms are also different. Microalgae mainly cooperate with detoxification through intracellular and extracellular processes. Higher plants rely more on root exudates or interact with rhizosphere microorganisms [44], while bacteria may form biofilms or efflux pump mechanisms [42].

Microalgae have formed a multi-level and multi-dimensional metal tolerance mechanism in the long-term evolution process, and the biosorption on the cell surface is the primary defense against heavy metals. When in the environment containing heavy metals, there are a variety of negatively charged functional groups on the surface of microalgae cells, such as carboxyl, hydroxyl, amino [45,46], these functional groups can react with metal ions by ion exchange, complexation or electrostatic adsorption [47,48]. Olivia [49] pointed out that a variety of functional groups on the surface of microalgae cell wall (such as hydroxyl, carboxyl, imino, etc.) are the main sites for heavy metal adsorption. Furthermore, the mechanisms of cell wall adsorption and chelation, intracellular binding of metallothionein to phytochelatins, and vacuolar compartmentation and efflux of metallothionein and phytochelatins have been proposed. These synergistic effects enable microalgae to survive and maintain normal physiological functions in metal-contaminated environments [50,51]. However, when microalgae are exposed to heavy metal ions such as Hg, Cu, and Pb in the environment, they will be subjected to heavy metal stress. Heavy metal ions can interfere with chloroplasts, bind to thylakoid membranes, and induce microalgae to produce ROS, causing oxidative damage [38]. In this process, the cell wall of microalgae is the first barrier against metal ions, and its surface is rich in negatively charged polysaccharides (e.g., cellulose, alginate), proteins, carboxyl and phosphate groups [52], quickly capture and immobilize metal ions through ion exchange, electrostatic adsorption or coordination [53]. Research by Cavalletti et al. demonstrated that polysaccharides derived from the cell wall of *Phaeodactylum tricornutum* are effective in adsorbing the heavy metal ions Cd^{2+} and Pb^{2+} [54]. The cell wall is rich in cysteine glycoproteins, which can form stable complexes with Hg^{2+} or Cu^{2+} through -SH, and can reduce the free concentration of heavy metals in the environment in a short time, thereby reducing the toxicity of heavy metals to microalgae cells. Under metal stress, microalgae produce extracellular polymeric substances (EPS) rich in polysaccharides, proteins, and other biomolecules. These substances contain abundant functional groups such as carboxyl, hydroxyl, and phosphoryl moieties that serve as active binding sites. Through chelation and surface complexation mechanisms, EPS immobilizes heavy metal ions near the cell surface. This extracellular sequestration prevents intracellular metal penetration while simultaneously enhancing the organism's overall biosorption capacity (Figure 1).

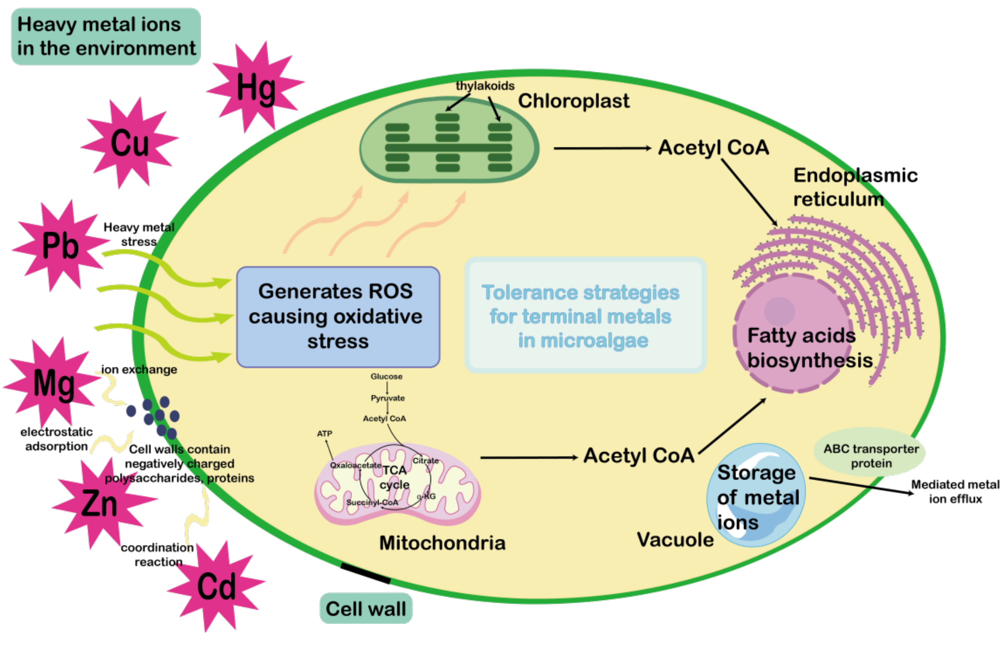

Figure 1. The possible mechanisms of microalgae tolerance to heavy metals.

The intracellular tolerance mechanism of microalgae to heavy metals is the core biological basis for its survival in polluted habitats. When heavy metal ions break through the extracellular barrier and enter the cell, microalgae rapidly activate the multi-level response mechanism with antioxidant defense system as the core [55]. Heavy metal stress often induces the production of ROS in microalgae cells. Excessive ROS can cause irreversible oxidative damage to biological macromolecules such as proteins, lipids and nucleic acids [38]. Therefore, the antioxidant enzyme system in microalgae cells, such as SOD, catalyzes O^{2-} disproportionation to produce H_2O_2. Subsequently, ascorbate peroxidase (APX) cooperates with glutathione-ascorbic acid cycle to reduce H_2O_2 to H_2O. Finally, ROS is converted into harmless substances to reduce oxidative damage [56]. Research has shown that to mitigate oxidative damage during acclimation, the acid-tolerant microalga *Graesiella* sp. MA1 upregulates its antioxidant defense system, including the activities of SOD and APX and the pool of glutathione (GSH) [57]. Moreover, cell metabolic remodeling also plays an important role in heavy metal tolerance. Mitochondrial

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tricarboxylic acid cycle and chloroplast carbon assimilation process produce acetyl coenzyme A, which acts as a precursor of fatty acid biosynthesis and promotes intracellular lipid synthesis [58]. These newly synthesized lipids not only participate in cell membrane repair, but also provide a material basis for compartmentalized isolation of heavy metal ions. Heavy metal ion tolerance is achieved through the action of specific transporter families, including ATP-binding cassette (ABC) transporters, *p*-type ATPases, and cation diffusion facilitator (CDF) transporters—which pump these ions into vacuoles for chelation or out of the cell, thereby reducing their toxic cytoplasmic concentrations [59]. Moreover, intracellular metal-binding proteins and small molecules constitute a precise detoxification system. MT is rich in cysteine residues and can form stable complexes with Cd^{2+} and Zn^{2+} through sulfhydryl groups [48], and on the basis of γ-(Glu-Cys)-Gly structure derived from GSH, and phytochelatin (PC) form high molecular weight complexes with heavy metal ions such as As^{3+} and Pb^{2+}, which can effectively alleviate the interference of heavy metal ions on cell metabolism by reducing the concentration of free heavy metal ions [60]. In summary, these intracellular tolerance mechanisms are synergistically regulated through signal transduction networks to form a complex and efficient heavy metal detoxification system, which enables microalgae to adapt to the environment of heavy metal pollution to a certain extent, and also provides a theoretical basis for the development of bioremediation technology based on microalgae.

3. Functional Characteristics of Phytohormone in Microalgae

3.1. Endogenous Phytohormone in Microalgae

Microalgae employ a spectrum of endogenous phytohormones as key regulatory mechanisms to govern their growth, metabolism, and stress responses [61]. Common classes of these signaling molecules include IAA, CKs, ABA, GAs, JAs, SA, and ethylene (Table 1). Specifically, IAA and CKs drive proliferation and biomass increase [62]. In response to environmental challenges, ABA and SA activate antioxidant defenses to counteract stresses like high salinity and heavy metals [63], whereas ethylene and JAs contribute to pathways that mitigate oxidative damage [64]. The role of GAs, while less characterized, appears to influence growth patterns in specific green algae. These hormones have concentration-dependent (low promotion and high inhibition) and synergistic/ antagonistic effects, such as IAA and CKs synergistically regulate proliferation, while ABA may inhibit the growth-promoting effects of IAA. In addition, environmental factors (such as nutrient limitation, light change) can dynamically affect hormone levels, thereby regulating the physiological adaptation mechanism of microalgae. Studying the endogenous hormones of microalgae not only helps to understand its environmental adaptability, but also provides a theoretical basis for optimizing algal culture [61].

Table 1. The Diverse Functions and Characteristics of Phytohormone in Microalgae.

Name	Feature	Function	Source
IAA	Main component is indole-3-acetic acid (IAA)	Regulate cell division and elongation, promote biomass accumulation	Ubiquity
CKs	Mainly isopentenyl adenine substances	Leading cell cycle progression and enhancing proliferation ability	Ubiquity
GAs	GA1, GA3 were detected in green algae.	Stimulate growth metabolism in some green algae	*Breviolum minutum*
ABA	Aromatic sesquiterpenes	Mediated abiotic stress (salinity / drought / heavy metals) defense	Ubiquity
SA	Phenylpropanoid metabolites	Activate the antioxidant system to alleviate oxidative damage	*Chlorella vulgaris*
JAs	Oxylipin derivatives	Participate in ROS clearance and damage repair mechanism	*Charophyte*
Ethylene	Gas hormone	Regulating cell differentiation and programmed cell death	*Glaucophytes*
Brassinolide (BRs)	Steroid	Affect cell wall remodeling and morphogenesis	*Hydrodictyon reticulatum*

3.2. Microalgae Phytohormone Types and Characteristics

3.2.1. Growth-Promoting Hormones

In microalgae, key growth-promoting hormones (IAA, CKs, GAs) exert central control over proliferation and metabolism. IAA promotes division, elongation, and biomass, and influences photosynthesis [65]; CKs regulate the cell cycle and chlorophyll synthesis to boost photosynthetic yield [66]; and GAs enhance growth in taxa like *Chlorella* [67]. These effects are often concentration-dependent (biphasic) [68], and involve synergistic crosstalk, as between IAA and CKs [69]. Understanding this network offers a strategy for improving cultivation efficiency.

3.2.2. Stress-Responsive Hormones

Stress-responsive hormones (such as ABA, SA and JAs) play a key role in microalgae response to environmental stress. ABA can activate the synthesis of antioxidant enzyme system (SOD, CAT) and osmotic adjustment substances, and enhance the resistance to heavy metal stress [70]. SA alleviated oxidative damage by inducing antioxidant metabolism and stress gene expression [71]; JAs are involved in ROS scavenging and membrane lipid repair to maintain cell integrity [72].

3.2.3. Developmental Regulatory Hormones

Developmental regulatory hormones (such as ethylene and BRs) are involved in cell differentiation, morphogenesis and life cycle transition of microalgae. Ethylene affects the balance of proliferation and differentiation by regulating cell cycle genes, and high concentration can induce programmed death [73]; BRs mainly regulate cell wall remodeling and morphological maintenance [74]. The coordination of these hormones with environmental cues (e.g., photoperiod and nutrition) orchestrates the complete developmental process in microalgae, from single-cell growth to population establishment, thereby illuminating a key aspect of their adaptive mechanism.

3.3.4. Conservatism and Uniqueness of Microalgae Hormone Signaling Pathway

The hormone signaling pathway is highly conserved in the process of biological evolution, and it is unique due to the adaptive evolution of species. In microalgae, the core components of the hormone regulatory network (e.g., receptors, signal transduction proteins, and downstream response factors) have significant homology with higher plants, indicating the ancient origin of their signaling pathways. Studies have shown that IAA and CK signaling pathways in microalgae depend on similar TIR1/AFB receptor and histidine kinase systems, which are highly similar to the regulatory mechanisms of terrestrial plants [75].

ABA regulates stress response through the PP2C-SnRK2 cascade in microalgae and higher plants, further confirming the conservation of the hormone signaling pathway [76]. From the molecular evidence, the function and physiological function of endogenous ABA in oil microalgae *Nannochloropsis oceanica* are similar to those of higher plants. In response to environmental stresses such as high salt or drought, ABA in higher plants can regulate stomatal closure to reduce water loss, and may also maintain intracellular water balance through similar signaling mechanisms in microalgae [61]. In the study of *C.vulgaris*, it was found that JA treatment had an effect on its growth and physiological characteristics. The growth was promoted within a certain concentration range, and the growth was inhibited beyond the range [77]. In higher plants, JA is also involved in plant growth, development and response to biotic and abiotic stresses, such as resistance to pests and diseases [78], regulation of flowering and other processes. This indicates that the dual regulation of JA on growth is conservative in microalgae and higher plants, which may affect the physiological activities of cells through similar signal transduction mechanisms.

While some hormonal signaling components, such as IAA response elements, are conserved, phylogenetic evidence shows that microalgae have lost many pathway elements found in terrestrial plants, highlighting their unique hormone response mechanisms [79]. A key example is the melatonin receptor-MAPK pathway, which exists in unicellular green algae but has been integrated into phytohormone signaling via distinct evolutionary trajectories in terrestrial plants and microalgae [80].

The signaling pathways in microalgae are often distinct and simplified, as exemplified by the finding that some cyanobacteria lack the typical ABA receptor PYR/PYL and utilize non-canonical pathways for ABA perception [81], The GA signaling pathway of some green algae(e.g., *Chlamydomonas*) may not depend on DELLA protein, suggesting that it independently evolved alternative regulatory mechanisms [82]. ROS in microalgae is not only a toxic molecule, but also a signaling molecule that activates specific pathways. Studies have found that under high concentration of cadmium stress, ROS activates the synthesis of non-enzymatic antioxidant systems (e.g., carotenoids and reduced glutathione) by inhibiting the activity of antioxidant enzymes (e.g., SOD). This ‘metabolic turn’ strategy is rare in higher plants [83]. Environmental stresses (such as nutrient deficiency, high light, extreme temperature, high salinity and heavy metals) can inhibit the growth and metabolite accumulation of microalgae, while phytohormone (such as ABA, BRs) can alleviate these negative effects by regulating cell growth, stress tolerance and lipid biosynthesis [84]. For example, ABA can coordinate the response of microalgae to environmental signals and enhance their stress recovery ability, while the combination of exogenous phytohormone and stress conditions can further promote the synthesis of metabolites and improve the stress resistance of microalgae; under the conditions of 20 °C and 10‰—20‰ salinity, the growth, arsenic accumulation and photosynthetic efficiency of microalgae reached the peak, and the cell morphology remained the best [85]. In addition, environmental factors such as culture agitation and temperature changes can affect chlorophyll concentration in a species-specific manner, and hormones may improve culture efficiency by optimizing these conditions [86].

In addition, the hormone signals of microalgae are often closely coupled with photosynthesis, biological rhythms and group behaviors(e.g., quorum sensing), showing an integration pattern different from that of multicellular plants[63]. When microalgae respond to metal stress, IAA signal will change membrane lipid composition to maintain membrane fluidity by regulating the expression of fatty acid desaturase gene. Studies have shown that under salt stress, the activation of peroxisome proliferation-related genes(e.g., PEX11) can promote lipid synthesis, and IAA signaling directs more resources to lipid accumulation rather than protein synthesis by regulating carbon flux distribution [87,88]. These findings indicate that the hormone signaling system not only retains the core framework in evolution, but also develops unique adaptive strategies in different lineages, providing important clues for understanding the origin and functional differentiation of phytohormone.

4. Regulation of Endogenous Phytohormones in Microalgae under Metal Stress

With the development of modern industry and the intensification of human activities, contamination by heavy metals such as Cd, Cu, and Pb is becoming increasingly serious, posing a serious threat to the survival and physiological functions of microalgae [89]. Phytohormones play a central regulatory role in the response of microalgae to heavy metal stress. When microalgae perceive heavy metal stress signals, endogenous or exogenous Phytohormone can activate their specific signaling pathways. Through complex interactions and signal integration between these pathways, a regulatory network is formed to coordinate various physiological metabolic processes of microalgae (such as antioxidant defense, metal ion transport, cell division and membrane stability maintenance, etc.), thereby systematically improving their tolerance to heavy metals. In-depth analysis of this regulatory network and its molecular mechanism mediated by phytohormone will provide a solid theoretical basis for the efficient bioremediation of water heavy metal pollution by microalgae.

4.1. Physiological Regulation of Phytohormones on Microalgae Response to Metals

Microalgae, as integral primary producers, are fundamental to the aquatic food web while also contributing significantly to essential ecological processes like the global carbon cycle and nitrogen fixation [90]. As an important signal molecule in microalgae, phytohormone play an important role in their physiological regulation in response to heavy metal stress. When microalgae perceive heavy metal stress signals, the phytohormone signaling pathway is rapidly activated to form a sophisticated regulatory network. Studies have shown that the IAA signaling pathway promotes cell elongation and division by up-regulating the expression of related genes, enhances the physical tolerance of microalgae cells to heavy metals, and optimizes intracellular material transport and distribution, indirectly improving the buffering capacity for heavy metal toxicity [90]. It has been reported that CKs affects the synthesis and localization of metal transporters by regulating the process of cell division and differentiation, finely regulates the distribution of heavy metal ions in cells, and reduces the damage of toxic ions to key organelles [91]. In addition, ABA is particularly critical in this process. By promoting lipid accumulation, it significantly enhances the stability of cell membranes, effectively resists the penetration and destruction of heavy metal ions, and participates in regulating the expression of metal transport genes, guiding heavy metal ions to transport or store in low-toxic areas [92,93].

Phytohormone form a dynamic and balanced regulatory network through complex signal interaction and synergy. Nguyen et al. [94] found that under the combined stress of multiple heavy metals, IAA, CK and ABA signaling pathways are intertwined to regulate the growth and metabolism, antioxidant defense and ion transport of microalgae [64]. While IAA promotes cell growth, it provides more cell space and material basis for the synthesis of metal transporters regulated by CK. The enhanced cell membrane stability of ABA provides a more stable internal environment for IAA and CK-mediated physiological activities [19,71]. This synergistic regulation ensures that microalgae can not only maintain basic growth and reproduction under heavy metal stress, but also minimize the toxic effects of heavy metals. In the future, with the in-depth application of molecular biology and genomics technology, it is expected to analyze this process more accurately from the aspects of gene expression regulation and hormone signal transduction network, and open up a new path for the protection of ecological environment and the development of ecological restoration technology.

4.2. Molecular Regulation of Phytohormone on the Response of Microalgae to Metals

Phytohormones play a key role in the molecular regulation of microalgae's response to metal stress. When stressed by heavy metals, microalgae lacking phytohormone involvement experience disturbances in their physiological state and limited growth. Conversely, the presence of phytohormones triggers specific hormone signal transduction pathways. The IAA signaling pathway functions to optimize microalgal cell morphology and structure by up-regulating genes responsible for cell elongation and division (Figure 2). A significant consequence of this growth promotion is an indirect enhancement of heavy metal tolerance. Furthermore, IAA signaling can reduce intracellular metal concentrations by increasing the cell wall's adsorption capacity [48,55]. This integrative mechanism is supported by the work of Piotrowska-Niczyporuk et al., who found that IAA and cytokinins coordinate growth and stress adaptation in *Scenedesmus obliquus* exposed to lead. The hormonal interplay led to marked changes in metabolites associated with metal chelation and glutathione synthesis, underpinning the detoxification response [17]. IAA can also induce the secretion of EPS. Polysaccharides and proteins in EPS further adsorb metal ions through complexation [95]. The ABA signaling pathway further enhances heavy metal stress resistance by promoting lipid accumulation, strengthening cell membrane stability, and regulating the expression of metal transport genes. These coordinated mechanisms collectively enable cells to better withstand heavy metal toxicity [92]. According to Verma et al. [96], ABA treatment significantly alleviates cadmium stress in cyanobacteria by upregulating the expression of SOD and CAT genes, stimulating GSH synthesis, and enhancing cellular redox balance. Furthermore, the ABA signaling pathway activates the transcription factor AREB/ABF through phosphorylation, enabling its binding to promoter regions of antioxidant enzyme genes and thereby inducing their expression [97]. Additionally, ABA can reduce metal ion uptake by regulating stomatal closure [in plants], providing an indirect mechanism for stress mitigation.

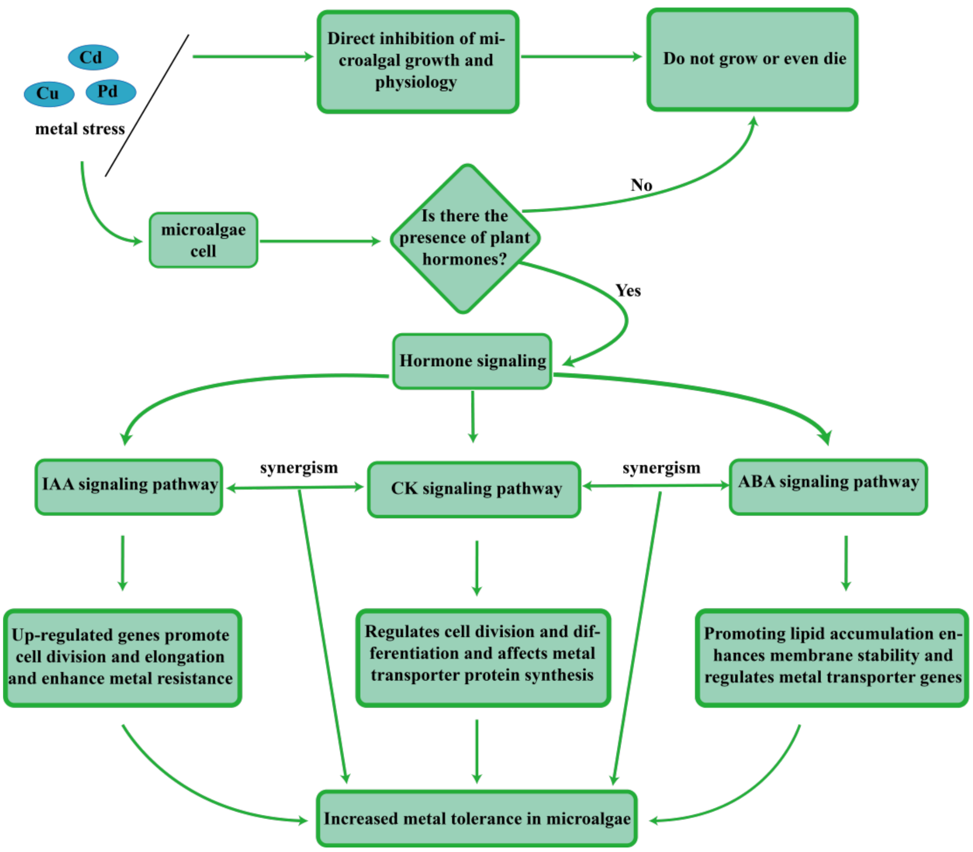

Figure 2. Molecular regulation pathway map of phytohormone-mediated microalgae response to metal stress.

Beyond IAA and ABA, JAs and ethylene also significantly regulate metal transporter expression through synergistic interactions. As demonstrated by Ibuto et al., the JA and ethylene signaling pathways cooperatively enhance copper tolerance under metal stress by concurrently upregulating the expression of the metal transporters NRAMP3 and ZIP4. Furthermore, this coordinated induction promotes transmembrane copper transport and facilitates its compartmentalization within intracellular stores, thereby effectively reducing metal toxicity in the cytoplasm [98,99]. It was found that JA formed a complex with EIN3/EIL1 protein in ethylene signaling pathway by activating V-myb avian myeloblastosis viral oncogene homolog transcription factor, and combined with the promoter region of NRAMP3 gene to enhance its transcriptional activity [100]. In addition, ethylene can also reduce the loss of intracellular metals by inhibiting the efflux pump of metal ions (such as the HMA family), thereby maintaining ion homeostasis [101]. Therefore, the molecular regulation mechanism of phytohormone on the response of microalgae to metal can not only help us understand the survival strategy of microalgae in polluted environment, but also provide a theoretical basis for the bioremediation of heavy metal pollution. Future integration of molecular biology with genomic and proteomic technologies will enable precise elucidation of phytohormone regulatory pathways at the molecular level. These advancements will provide critical scientific foundations for enhancing water ecosystem protection and pioneering novel bioremediation strategies.

5. Applications and Challenges

5.1. Bioremediation Technology Development

Bioremediation of heavy metal-contaminated water represents a critical challenge in contemporary environmental governance. Microalgae, possessing advantages including rapid growth, strong bioaccumulation capacity, and scalable cultivation, have emerged as a prominent research focus in this field [102,103]. As core regulatory factors in microalgal responses to heavy metal stress, phytohormones can systematically enhance tolerance, bioaccumulation efficiency, and environmental adaptability through exogenous pretreatment. Supporting this, Piotrowska-Niczyporuk [70] demonstrated that exogenous application of IAA and CKs significantly increases both cellular antioxidant content and the activity of ROS-scavenging enzymes, including SOD, CAT, APX, and glutathione reductase, thereby strengthening microalgal resistance to Pb toxicity.

The symbiotic system formed by algae and bacteria significantly improves the efficiency of heavy metal pollution remediation through hormone signal interaction. The synergistic mechanism mainly includes hormone-mediated metabolic regulation and enhanced stress resistance. Recent studies have shown that phytohormone (such as IAA, CKs, ABA, etc.) play a key role in algae-bacteria interaction and achieve functional complementation through cross-talk. *Chlorella* was co-cultured with *Azospirillum brasiliensis* under copper stress conditions and found that similar to the exogenous IAA group, they all produced significant mitigation effects, which may be related to the secretion of IAA [104].

5.2. Phytohormones Synergistic Genetic Engineering to Strengthen Microalgae Repair

The regulatory mechanism of phytohormone in response to heavy metal stress in microalgae is mainly reflected in two levels: physiological metabolism and molecular regulation. Studies have shown that exogenous phytohormone can effectively remove excessive ROS induced by heavy metal stress by activating the antioxidant defense system of microalgae, thereby maintaining cell redox homeostasis [105]. Specifically, IAA, CKs and other hormones can reduce the level of lipid peroxidation and enhance the stability of cell membrane system by regulating the activity of antioxidant enzymes such as SOD and peroxidase [71]. At the same time, stress-responsive hormones such as ABA can regulate the expression of heavy metal transporters, promote the compartmentalized storage of heavy metals in vacuoles through chelation, and reduce their cytotoxicity [64]. By precisely regulating the concentration and combination ratio of hormones, the enrichment ability of microalgae to heavy metals such as cadmium and lead can be improved while maintaining its growth activity, which provides a theoretical basis for algae remediation technology of polluted water [106].

The engineering of phytohormone metabolic networks is a cornerstone of genetic strategies to boost stress resistance in microalgae. This typically involves elevating endogenous hormone levels via the heterologous expression of key biosynthetic enzymes (e.g., YUCCA) or the knockout of degrading enzymes (e.g., cytokinin oxidase). As a result, downstream stress-response pathways are potentiated. Supporting this concept, overexpression of the metal tolerance protein gene *CrMTP4* was shown to maintain growth in engineered algae subjected to 0.5 mM Cd^{2+} [107]. The mechanism involved in the protein-mediated vacuolar compartmentalization of cadmium ions and enhanced glutathione metabolism [79]. Such technological breakthroughs provide new ideas for the construction of efficient heavy metal remediation engineering algae strains, but it is necessary to pay attention to the ecological safety assessment of gene operations.

5.3. Current Bottlenecks and Future Prospects

The difference of hormone signaling pathway among microalgae species significantly restricts its industrial application. Studies have shown that the response of different microalgae to hormones is species-specific. For the industrial cultivation of microalgae, a tailored analysis of the phytohormone network in the target species is imperative. This necessity arises from fundamental species-specific differences in how phytohormones regulate processes like fatty acid production [108] and biomass accumulation [66], reflecting the distinct evolution of these pathways in microalgae [61]. Neglecting this specificity by applying cross-species insights risks metabolic imbalance, thereby undermining productivity and significantly increasing the cost and complexity of scaling up.

Within industrial microalgae cultivation systems, pH and salinity critically modulate hormone-mediated responses to metal stress through physicochemical-biological coupling (Figure 3). Specifically, pH regulates metal ion adsorption kinetics by altering microalgal cell surface charge properties, while salinity influences metal bioavailability through ionic competition and complexation processes. These abiotic factors thereby fine-tune phytohormone signaling pathways that govern cellular detoxification mechanisms. The acidic environment can induce cells to secrete metabolites such as organic acids to alleviate metal toxicity [109,110]. Salinity interferes with ion homeostasis by regulating osmotic pressure. For example, under the condition of low salinity and high silicon, the increase of cell wall functional group abundance can enhance the adsorption capacity of cadmium and copper [111]. However, the synergistic regulatory mechanism of salinity gradient on hormone signal transduction (such as ABA synthase activity) and metal transporter expression is still unclear. It is necessary to combine transmembrane ion flow analysis and transcriptomics to reveal its molecular interaction network [112], this is of great significance to the development of precise restoration technology for complex water environment.

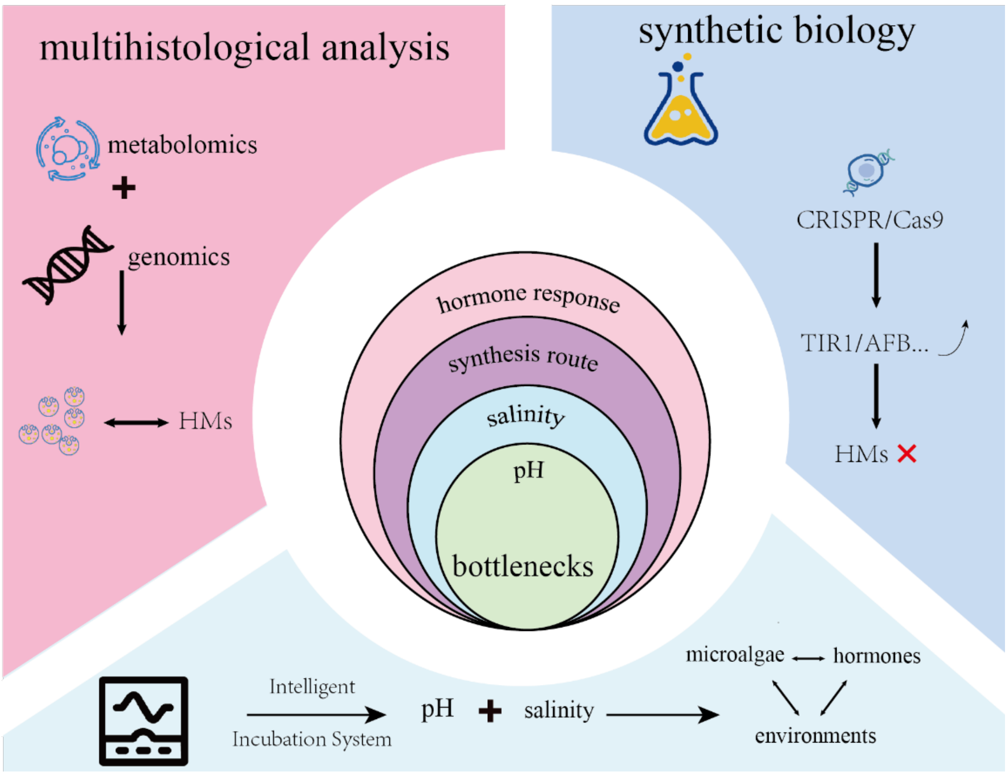

Figure 3. Microalgal stress response mechanisms and the integration challenges/solutions in multi-omics and synthetic biology approaches.

Future research should prioritize systems biology approaches to construct comprehensive models of phytohormone-metal interactions in microalgae by integrating genomic and metabolomic data. This foundational work will enable the targeted manipulation of stress-resistance pathways using synthetic biology tools, such as CRISPR/Cas9-mediated editing of key hormone biosynthesis genes. Concurrently, integrating these biological advances with intelligent cultivation systems (Figure 3) will allow for the dynamic feedback control of critical parameters like pH and salinity. To accelerate translation, it is essential to develop bioinformatics-driven platforms for predicting species suitability, thereby identifying optimal 'microalgae-hormone-environment' combinations. This multi-faceted strategy is crucial for overcoming the scaling challenges of bioremediation technologies and developing highly effective, ecologically sustainable solutions for mitigating heavy metal pollution.

Author Contributions

H.G.: formal analysis, investigation, writing—review & editing; L.C., Y.K. and N.Y.: writing–review & editing; X.Y.: conceptualization, methodology, resources, writing—review & editing, project administration; R.R.: conceptualization, methodology, formal analysis, investigation, writing—review & editing, supervision; P.C.:

conceptualization, methodology, formal analysis, investigation, writing—original draft, writing & review. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

Data will be made available on request.

Conflicts of Interest

The authors declare no conflict of interest. Given the role as Editorial Board Member, Pengfei Cheng and Roger Ruan had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

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