JOURNAL OF HEAVY METAL RESEARCH

https://jhmr.hsu.ac.ir E-ISSN: 3116-0522 Journal of Heavy Metal Research, 2026, vol 1, Issue 2, 20-29

Review Article

The Pivotal Role of Heavy Metals in Protein Structure and Function: A Brief Review

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Received: 29 November 2025
Revised: 26 February 2026
Accepted: 11 May 2026
Published: 12 May 2026

Publisher: Hakim Sabzevari University

Citation: Khawarat, R., & Noor Qureshi, A. (2026). The Pivotal Role of Heavy Metals in Protein Structure and Function: A Brief Review. *Journal of Heavy Metal Research, 1*(2), 20–29.

Abstract

Metal ions are integral to biological chemistry, underpinning structural organization, catalytic reactivity, and regulatory control in living systems. Current estimates indicate that roughly one-third of all proteins require a bound metal cofactor to achieve functional competence. This review examines the roles of selected first-row transition metals, nickel (Ni), chromium (Cr), zinc (Zn), copper (Cu), manganese (Mn), and cobalt (Co), in protein structure and function, emphasizing the mechanistic principles that govern their biological activity. We analyze how metal coordination shapes protein folding landscapes, stabilizes native conformations, and enables small structural domains such as zinc fingers to attain functional architecture. In contrast, we discuss how aberrant metal binding to unfolded or non-native states can disrupt folding pathways, promote aggregation, and contribute to proteotoxic stress. The catalytic versatility of these metals is explored in the context of metalloenzymes, where redox cycling and Lewis acid chemistry facilitate reactions ranging from energy metabolism to antioxidant defense. Additionally, we highlight the role of metal-responsive transcription factors that couple intracellular metal availability to gene expression, thereby maintaining homeostatic balance. Finally, we examine the pathological consequences of metal dyshomeostasis, including carcinogenesis, neurodegeneration, and cardiovascular toxicity. Together, these perspectives underscore the delicate equilibrium between essential metal utilization and metal-induced toxicity that defines metal–protein interactions in health and disease.

Keywords: Metalloprotein, Protein Folding, Metal Homeostasis, Metalloenzyme, Transcription Factor, Nickel, Metal Toxicity

1. Introduction

Metal–protein interactions represent a fundamental aspect of cellular chemistry and have long been recognized as essential to biological function. Current bioinformatic and structural analyses suggest that approximately 30–50% of proteins depend on a bound metal ion for catalytic activity, structural integrity, or regulatory control (Andreini et al., 2008; Shi & Chance, 2011). These metalloproteins participate in a wide range of core cellular processes, including DNA replication and repair, transcriptional regulation, intermediary metabolism, redox homeostasis, and intracellular signaling (Bertini et al., 2007).

The chemical versatility of metal ions underlies this functional breadth. Unlike amino acid side chains, metals can access multiple oxidation states, adopt diverse coordination geometries, and function as strong Lewis acids or redox centers. These properties enable proteins to catalyze reactions and stabilize structures that would otherwise be chemically inaccessible within the

constraints of the canonical twenty amino acids (Foster et al., 2022).

The designation "heavy metals" refers to a loosely defined group of elements, many of which include first-row transition metals that are required at trace levels yet become toxic when intracellular concentrations exceed physiological thresholds (Tamás et al., 2014). In this review, we focus on six biologically relevant metals—nickel (Ni), chromium (Cr), zinc (Zn), copper (Cu), manganese (Mn), and cobalt (Co)—whose roles exemplify this duality between essentiality and toxicity.

Their biological function depends on tight quantitative and spatial regulation. Cells have therefore evolved coordinated networks of membrane transporters, metallochaperones, buffering ligands, and storage proteins to maintain metal homeostasis and to ensure accurate metalation of target apoproteins (Foster et al., 2022). Such specificity is not trivial. The intrinsic binding affinities of divalent transition metals to common protein ligands generally follow the Irving–Williams series:

$Mg(II) < Mn(II) < Fe(II) < Co(II) < Ni(II) < Cu(II) > Zn(II)$.

This thermodynamic hierarchy presents a persistent challenge, as metals with higher affinity could potentially displace cognate, lower-affinity ions from metalloproteins. Consequently, cells must actively control metal availability to prevent mismetalation while still permitting efficient cofactor insertion.

Conversely, excessive exposure to essential metals or the introduction of non-essential metals can overwhelm cellular buffering and trafficking systems, resulting in toxicity. One of the central molecular consequences of such dysregulation is the impairment of protein structure and function. Toxic metals may displace native cofactors from metalloenzymes, bind inappropriately to reactive functional groups—particularly thiol residues—or promote oxidative modifications of amino acid side chains through redox cycling and reactive oxygen species (ROS) generation (Witkowska et al., 2021; Tamás et al., 2014).

Beyond these well-established mechanisms, increasing evidence indicates that metal ions can directly perturb the protein folding landscape. By stabilizing non-native intermediates or forming aberrant coordination complexes with partially unfolded polypeptides, metals can divert folding pathways toward kinetically trapped states, ultimately promoting misfolding and aggregation (Hartwig & Schwerdtle, 2002; Tamás et al., 2014). This folding interference represents a critical, and often underappreciated, dimension of metal-induced proteotoxicity.

This review examines the dualistic behavior of selected heavy metals within protein systems. We begin by analyzing their constructive roles in stabilizing protein architecture and guiding folding processes. We then evaluate their functional contributions to enzymatic catalysis and transcriptional regulation, emphasizing representative metalloenzymes and metal-responsive regulatory proteins.

Subsequently, we consider the broader physiological and pathological consequences of metal–protein interactions, highlighting how tightly regulated homeostasis sustains cellular integrity, whereas dysregulation contributes to disease development. By integrating structural, mechanistic, and biological perspectives, this work aims to clarify the complex interplay between essential metal utilization and metal-induced toxicity in protein biology.

2. Structural Roles of Metal Ions in Proteins

The acquisition of a stable, three-dimensional conformation is a prerequisite for the function of most proteins. Metal ions play a fundamental role in this process, acting as structural linchpins that organize polypeptide chains into precise architectures. This structural contribution ranges from guiding the folding pathway to stabilizing the final native state. However, this same chemical reactivity can become detrimental, leading to misfolding and aggregation when metal-protein interactions are not properly controlled.

2.1. Metal-Induced Protein Folding and Stability

A central issue in metalloprotein biogenesis concerns the timing of metal incorporation relative to polypeptide folding, whether metal binding precedes, accompanies, or follows the acquisition of tertiary structure. In many systems, the metal ion does not simply stabilize a preformed fold but actively shapes the folding pathway itself. Experimental evidence indicates that metal coordination can lower kinetic barriers or alter the thermodynamic landscape, thereby facilitating productive folding trajectories (Arnesano et al., 2005).

For example, in vitro studies of copper-binding proteins have shown that coordination of Cu(I) or Cu(II) to an unfolded or partially folded polypeptide can markedly accelerate the attainment of the native state by several orders of magnitude compared with folding of the apoprotein followed by subsequent metal insertion (Palm-Espling et al., 2012). These observations support a model in which the metal ion acts as a structural

template, stabilizing early folding intermediates and steering the polypeptide toward its functional conformation.

In addition to influencing folding kinetics, metal ions contribute substantially to the thermodynamic stability of the mature protein. Coordination bonds formed with side chains such as histidine, cysteine, aspartate, or glutamate create intra-molecular cross-links that restrict conformational freedom and reduce the entropy of the unfolded ensemble (Tanaka et al., 2004). The resulting stabilization enhances resistance to thermal fluctuations, denaturation, and proteolytic degradation, thereby preserving protein integrity under physiologically dynamic conditions.

2.2. The Archetypal Structural Role of Zinc: Zinc Finger Proteins

The most prominent example of a metal serving a purely structural role is found in zinc finger proteins (ZNFs). ZNFs represent one of the largest and most diverse protein superfamilies, constituting nearly 5% of the human genome (Kamaliyan and Clarke, 2024). In these proteins, a zinc ion is coordinated by a combination of cysteine and/or histidine residues, creating small, independently folded domains (Krishna et al., 2003). The most common is the Cys2His2motif. The Zn(II) ion is redox-inactive and its role is exclusively structural; it is essential to stabilize the "finger" motif, which would otherwise be too small to fold on its own (Cassandri et al., 2017). This stable scaffold provides the necessary stability and flexibility for ZNFs to bind to a wide variety of substrates, including DNA, RNA, proteins, and lipids, thereby participating in a vast range of cellular processes such as transcriptional regulation, DNA repair, and chromatin remodeling (Kamaliyan and Clarke, 2024; Padjasek et al., 2020).

2.3. The Dark Side: Metal-Induced Misfolding and Aggregation

Although metal coordination is indispensable for many proteins, it can be highly disruptive when occurring outside its native structural context. Proteins in partially folded or fully unfolded states present flexible backbones and solvent-exposed side chains, rendering them particularly vulnerable to non-specific metal binding (Tamás et al., 2014). In such conformations, metal ions encounter accessible coordination sites that are normally buried or sterically constrained in the native fold.

Toxic metals such as cadmium (Cd(II)) and mercury (Hg(II)), as well as metalloids including arsenite (As(III)), exhibit strong affinity for electron-donating functional groups. These species readily form stable multidentate complexes with thiol groups of cysteine, imidazole nitrogens of histidine, and carboxylate groups of aspartate or glutamate residues (Hartwig & Schwerdtle, 2002). Because these interactions often outcompete native intramolecular contacts, they can stabilize aberrant conformations or cross-link polypeptide chains, thereby perturbing normal folding pathways.

The formation of such aberrant metal–protein complexes can stabilize non-native conformations and effectively trap the polypeptide in misfolded states, preventing productive progression toward the thermodynamically favored native structure. Experimental studies have demonstrated that several heavy metals inhibit the in vitro refolding of chemically denatured proteins at nanomolar concentrations, with IC_{50} values frequently in the low to mid-nanomolar range (Tamás et al., 2014). These findings underscore the high affinity of toxic metals for exposed coordination sites within unfolded or partially folded intermediates.

Mechanistically, this inhibition reflects the creation of kinetic traps along the folding landscape. Stable, non-physiological metal coordination restricts conformational rearrangements, diverts folding intermediates away from native trajectories, and in some cases promotes intermolecular cross-linking. The resulting accumulation of misfolded species increases the likelihood of oligomerization and aggregate formation, many of which exhibit cytotoxic properties (Sharma et al., 2008). Such metal-induced perturbations of the folding process represent a major pathway of proteotoxic stress. By overwhelming chaperone systems and disrupting protein quality control networks, these events compromise cellular proteostasis and viability. Increasing evidence links this mechanism to the pathogenesis of protein aggregation disorders, including Alzheimer's and Parkinson's diseases, in which metal dyshomeostasis and aberrant metal–protein interactions contribute to disease progression (Tamás et al., 2014; Roberts et al., 2012).

3. Functional Roles of Metal Ions in Proteins

Beyond their structural contributions, metal ions are at the heart of protein function, serving as indispensable catalytic cofactors in metalloenzymes and as key regulators of cellular processes like signal transduction and gene expression. Their unique electronic properties enable chemical transformations and regulatory switches that are inaccessible to amino acid side chains alone.

3.1. Metals as Catalytic Cofactors in Metalloenzymes

Metalloenzymes harness the Lewis acidity and redox capabilities of metal ions to catalyze a vast spectrum of biochemical reactions. The protein environment fine-tunes

the metal's reactivity, creating a highly specific and efficient catalytic center (Andreini et al., 2008).

3.1.1. Nickel (Ni)

Although nickel is not utilized in mammalian metalloenzymes, it serves as an essential cofactor in a wide range of enzymes from archaea, bacteria, and certain plants, where it supports energy metabolism, carbon cycling, and, in some pathogens, virulence (Alfano & Cavazza, 2020). Nickel-dependent enzymes can be broadly categorized into non-redox and redox classes according to their catalytic chemistry.

In non-redox systems such as urease, Ni(II) functions primarily as a Lewis acid. By coordinating and polarizing the urea substrate, the metal center facilitates nucleophilic attack and subsequent hydrolysis. In gastric pathogens such as Helicobacter pylori, urease-mediated urea degradation generates ammonia, buffering gastric acidity and enabling colonization of the host (Boer et al., 2014).

In contrast, redox-active nickel enzymes exploit the metal's capacity to access multiple oxidation states. In [NiFe]-hydrogenases, nickel participates directly in the reversible oxidation of molecular hydrogen (H_2), mediating electron transfer within complex metalloclusters. Similarly, the CO dehydrogenase/acetyl-CoA synthase (CODH/ACS) complex contains a sophisticated Ni–Fe–S cluster that catalyzes CO_2 reduction and acetyl-CoA formation—key steps in microbial carbon fixation pathways (Can et al., 2014; Alfano & Cavazza, 2020). In these systems, nickel is integrated into highly organized active-site architectures that precisely tune its redox potential and reactivity.

The diversity of nickel coordination environments in representative enzymes is illustrated in Figure 1.

3.1.2. Copper (Cu)

Copper is an essential redox-active metal found in enzymes that are critical for aerobic life. Its ability to cycle between Cu(I) and Cu(II) states makes it ideal for mediating electron transfer reactions, particularly those involving oxygen. Prominent cuproenzymes include cytochrome c oxidase, the terminal enzyme in the mitochondrial electron transport chain; Cu, Zn-superoxide dismutase (Cu, Zn-SOD), which detoxifies superoxide radicals; and dopamine β-hydroxylase, which is vital for neurotransmitter synthesis (Ruiz et al., 2021; Sharma et al., 2023). Multicopper oxidases, such as ceruloplasmin, contain multiple copper centers and are crucial for iron homeostasis by oxidizing Fe(II) to Fe(III) for transport by transferrin (Li et al., 2023). The regulatory architecture of NikR in H. pylori is schematically summarized in Figure 2.

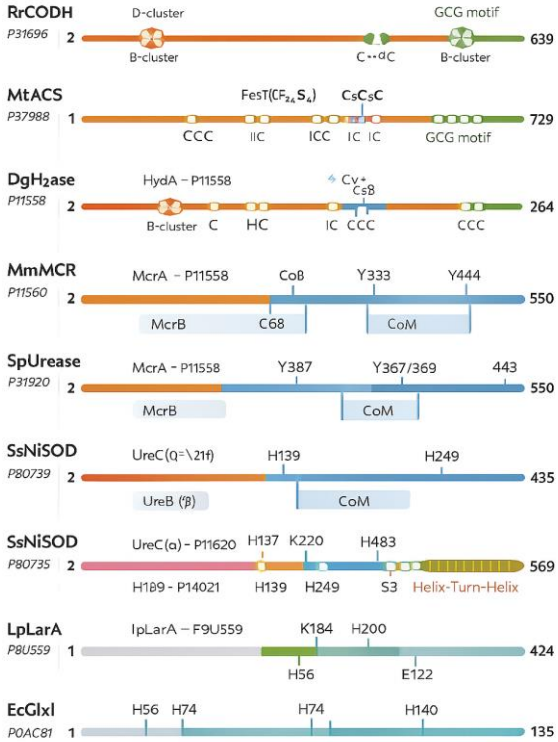

Figure 1. Domain organization and metal-binding motifs of representative Ni-dependent enzymes. The schematic highlights the diversity of nickel coordination environments, including complex cluster-type active sites (e.g., CODH/ACS and [NiFe]-hydrogenase) and mononuclear Ni centers (e.g., urease and Ni-SOD). Conserved cysteine, histidine, and other metal-coordinating residues are indicated. Adapted and modified from Alfano & Cavazza (2020).

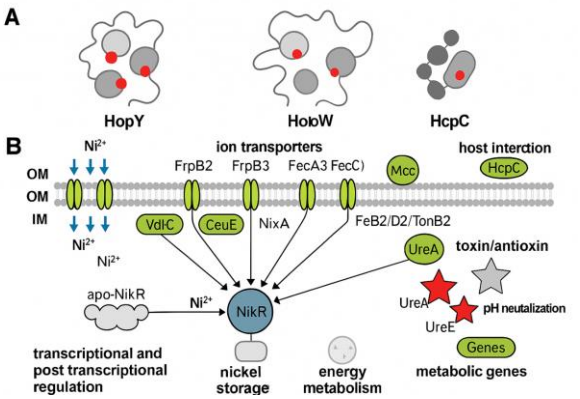

Figure 2. Schematic representation of the NikR regulatory network in Helicobacter pylori. Nickel (Ni(II)) uptake through membrane transport systems promotes formation of holo-NikR, the metal-bound active form of the transcription factor. Ni(II)-dependent allosteric activation enhances DNA binding to specific promoter regions, resulting in coordinated transcriptional regulation. This includes repression of nickel import genes to prevent metal overload and activation of virulence-associated genes, such as urease, which facilitates pH buffering in the gastric environment. The regulatory network

further influences genes involved in nickel storage, energy metabolism, and broader metabolic pathways. Adapted and modified from Conti et al. (2017).

3.1.3. Manganese (Mn)

Manganese is a redox-active transition metal that functions as an essential cofactor in enzymes involved in oxidative stress defense and intermediary metabolism. One of the most extensively characterized Mn-dependent enzymes is manganese superoxide dismutase (MnSOD), localized in the mitochondrial matrix. MnSOD protects against oxidative damage by catalyzing the disproportionation of superoxide radicals ($O_2^{\bullet -}$) through a redox cycle alternating between Mn(II) and Mn(III) states (Azadmanesh & Borgstahl, 2018). By maintaining mitochondrial redox balance, MnSOD plays a critical role in preserving cellular viability under conditions of elevated reactive oxygen species (ROS).

Beyond its role in antioxidant defense, manganese occupies a central position in photosynthetic oxygen evolution. In photosystem II, a tetranuclear Mn_4CaO_5 cluster within the oxygen-evolving complex (OEC) catalyzes the stepwise oxidation of water, leading to molecular oxygen formation. This process, driven by light-induced charge separation, represents one of the most fundamental redox reactions in biology and underpins the maintenance of atmospheric oxygen (Bertini et al., 2007).

Additional Mn-dependent enzymes further illustrate the metal's metabolic versatility. Pyruvate carboxylase requires Mn(II) for proper catalytic function in gluconeogenesis, while prolidase utilizes manganese in peptide bond hydrolysis during collagen turnover and extracellular matrix remodeling (Linus Pauling Institute, 2015). Collectively, these examples highlight manganese as a multifunctional redox cofactor whose biochemical roles extend from cellular antioxidant defense to global biogeochemical processes.

3.1.4. Cobalt (Co)

In mammals, cobalt exerts its biological function almost exclusively as the central metal ion in cobalamin (vitamin B_{12}). The distinctive chemistry of the cobalt–corrin macrocycle enables the reversible formation and cleavage of a cobalt–carbon (Co–C) bond, a rare example of stable organometallic reactivity in biological systems (Warren et al., 2021). This organometallic capability underlies the catalytic versatility of cobalamin-dependent enzymes.

Two principal reaction classes are mediated by distinct cobalamin derivatives. Adenosylcobalamin-dependent enzymes, such as methylmalonyl-CoA mutase, initiate catalysis through homolytic cleavage of the Co–C bond, generating a 5′-deoxyadenosyl radical. This highly reactive intermediate drives carbon-skeleton rearrangements via radical-based isomerization mechanisms. In contrast, methylcobalamin-dependent enzymes, including methionine synthase, exploit the exceptional nucleophilicity of the Co(I) state to facilitate methyl group transfer reactions. In this context, cobalt cycles between oxidation states to mediate heterolytic bond cleavage and reformation during one-carbon metabolism (Banerjee & Ragsdale, 2003; Warren et al., 2021).

Thus, cobalt in vitamin B_{12} represents a unique intersection between inorganic coordination chemistry and organometallic catalysis, enabling reaction pathways that are inaccessible to other biologically utilized metals.

3.2. Metals in Regulation and Signal Transduction

Beyond their catalytic and structural roles, metal ions can function as dynamic regulatory signals that modulate protein activity and gene expression. In many organisms, intracellular metal availability is sensed by specialized transcription factors that undergo conformational changes upon metal binding. This allosteric coordination event alters DNA-binding affinity or promoter selectivity, thereby adjusting transcriptional output in response to fluctuations in metal concentration.

Through such mechanisms, metal-responsive regulators coordinate the expression of genes encoding transporters, chaperones, storage proteins, and detoxification systems, maintaining homeostatic balance. In this way, metal ions operate not merely as cofactors but as integral components of signal transduction networks that couple cellular metal status to transcriptional control.

3.2.1. Nickel (Ni) and the NikR Transcription Factor

In many bacterial species, the nickel-responsive transcription factor NikR functions as a central regulator of nickel homeostasis. In the gastric pathogen Helicobacter pylori, NikR is indispensable for both survival and virulence, reflecting the organism's reliance on nickel-dependent enzymes such as urease (Conti et al., 2017).

In its metal-free (apo) form, NikR exhibits relatively low affinity for DNA. Coordination of Ni(II) at specific high-affinity metal-binding sites induces conformational rearrangements that enhance structural rigidity and promote formation of a DNA-binding–competent state (Baksh et al., 2023). This allosteric activation increases the affinity of holo-NikR for conserved promoter sequences, commonly referred to as NikR boxes.

Upon binding to these regulatory elements, NikR modulates transcription of genes involved in nickel

acquisition, utilization, and detoxification. For example, it represses expression of nickel import systems (e.g., nixA) under conditions of metal sufficiency to prevent toxicity, while activating genes required for acid adaptation, including urease, when nickel availability supports enzymatic function (Conti et al., 2017; Baksh et al., 2023). Through this metal-dependent switch, NikR integrates intracellular nickel status with transcriptional programs critical for environmental adaptation.

3.2.2. Chromium (Cr) and Transcriptional Interference

Chromium occupies a particularly complex position in biological chemistry. Trivalent chromium (Cr(III)) has been proposed to enhance insulin receptor signaling and glucose metabolism; however, its classification as an essential micronutrient remains controversial and insufficiently supported by definitive biochemical evidence (Vincent, 2000; O'Connell, 2023). In contrast, hexavalent chromium (Cr(VI)) is a well-established human carcinogen.

Following cellular uptake, typically via anion transport systems that mistakenly recognize chromate, Cr(VI) undergoes intracellular reduction through intermediates such as Cr(V) and Cr(IV), ultimately yielding Cr(III). This reductive process generates reactive oxygen species and contributes to oxidative stress. The resulting Cr(III), characterized by strong ligand-binding affinity and slow ligand-exchange kinetics, forms stable Cr–DNA adducts and protein–DNA crosslinks (Zhitkovich, 2011). These lesions can obstruct replication and transcription machinery, impair DNA repair processes, and alter chromatin structure.

Chromium exposure has also been shown to disrupt transcriptional regulation directly. Cr-derived DNA damage and crosslinking events interfere with the binding of transcription factors to their cognate sequences. For example, Cr(VI) exposure has been reported to inhibit NF-κB transcriptional activity, perturb Sp1-dependent gene expression, and disrupt CTCF-mediated chromatin insulation, leading to widespread transcriptional dysregulation (Wang et al., 1999; VonHandorf et al., 2018). Through these combined mechanisms, oxidative damage, crosslink formation, and epigenetic interference, chromium contributes to genomic instability and carcinogenic transformation.

3.2.3. Transcriptional Regulation by Other Metals

Comparable metal-responsive regulatory circuits operate for other biologically relevant transition metals. Although zinc finger transcription factors rely structurally on Zn(II) for domain stability, they function as central regulators of gene expression across diverse cellular pathways (Cassandri et al., 2017). In these systems, zinc serves not as a dynamic signal but as an essential architectural element that enables sequence-specific DNA recognition.

In contrast, copper-responsive transcription factors such as CopR in bacteria act as metal sensors. By directly coordinating Cu(I) or Cu(II), these regulators undergo conformational changes that alter promoter binding and modulate the transcription of genes encoding copper importers, efflux pumps, and detoxification proteins (Grünberger et al., 2021). Through this feedback control, cells rapidly adjust copper flux to maintain redox balance and prevent oxidative damage.

Similarly, manganese-responsive regulators including MntR coordinate Mn(II) to control expression of manganese transport systems (Barrows et al., 2024). This regulation ensures sufficient manganese availability for essential enzymes such as Mn-dependent superoxide dismutase, while preventing intracellular accumulation that could disrupt metal homeostasis. Collectively, these examples illustrate how transition metals function not only as catalytic cofactors but also as integral components of transcriptional control networks that preserve cellular metal balance.

4. Biological Implications and Disease

Metal–protein interactions exert far-reaching effects on cellular physiology and human health. Because transition metals participate in essential structural, catalytic, and regulatory processes, their intracellular concentrations must be tightly controlled within narrow limits. Both deficiency and excess disrupt biochemical equilibrium, leading to functional impairment at the molecular and cellular levels.

Perturbation of metal homeostasis and the resulting alterations in metal–protein interactions have emerged as a recurring mechanistic theme across diverse pathologies. Aberrant metal distribution, mismetalation of proteins, and redox imbalance contribute to disease processes ranging from neurodegenerative disorders to carcinogenesis and cardiovascular dysfunction. Thus, maintaining metal equilibrium is not merely a metabolic requirement but a central determinant of cellular integrity and long-term physiological stability.

4.1. Metal Homeostasis: A Tightly Regulated Cellular Network

To reconcile the essential biochemical functions of transition metals with their inherent cytotoxic potential, cells maintain tightly regulated metal management systems collectively referred to as the metallome. This network

comprises membrane transporters that control metal uptake and efflux, metallochaperones that direct specific metal ions to cognate apoproteins, and storage or buffering proteins that sequester excess metal pools (Tamás & Martinoia, 2005).

A defining feature of this system is the maintenance of exceedingly low concentrations of labile or "free" metal ions within the cytosol. By minimizing unbound metal species, cells reduce the likelihood of off-pathway coordination events and mismetalation driven by thermodynamic preferences (Foster et al., 2022). Metal distribution is therefore governed not solely by intrinsic binding affinities but by kinetic control and spatial compartmentalization.

For example, the copper chaperone Atox1 mediates targeted delivery of Cu(I) to proteins within the secretory pathway, shielding the metal from nonspecific interactions and preventing redox-mediated cytotoxicity (Palm-Espling et al., 2012). Similarly, dedicated nickel chaperones and accessory assembly factors orchestrate the insertion of Ni(II) into complex metallocenters such as those found in [NiFe]-hydrogenase, ensuring correct cluster maturation and catalytic competence (Zamble et al., 2017).

Through these coordinated mechanisms, cells achieve selective metalation while avoiding the deleterious consequences of uncontrolled metal reactivity.

4.2. Metal Toxicity and Carcinogenesis

When cellular buffering and trafficking systems are overwhelmed by excessive exposure, transition metals can exert pronounced toxic and carcinogenic effects. Although the molecular pathways differ among metals, a recurring theme involves oxidative stress, disruption of DNA integrity, and interference with regulatory networks governing cell proliferation and survival.

Nickel (Ni)

Nickel compounds are classified as Group 1 human carcinogens by the International Agency for Research on Cancer (IARC, 2012), with inhalation exposure posing particular risk to the respiratory tract. Nickel-induced carcinogenesis is multifactorial. One major mechanism involves the generation of reactive oxygen species (ROS), resulting in oxidative DNA damage and genomic instability. In addition, nickel interferes with DNA repair pathways and epigenetic regulation.

A distinctive feature of nickel toxicity is its ability to induce a "hypoxia-mimetic" response. Nickel exposure stabilizes hypoxia-inducible factor-1α (HIF-1α), even under normoxic conditions, leading to aberrant activation of hypoxia-responsive genes (Salnikow et al., 2003; Genchi et al., 2020). This dysregulation promotes altered cellular metabolism, angiogenesis, and survival signaling—processes closely associated with tumor progression.

Chromium (Cr)

Hexavalent chromium (Cr(VI)) is a potent human carcinogen whose toxicity is closely linked to its intracellular redox cycling. After cellular entry—often via sulfate transport pathways—Cr(VI) undergoes stepwise reduction to Cr(III). This process generates ROS and reactive intermediates that damage DNA, proteins, and membrane lipids (Zhitkovich, 2011).

The resulting Cr(III), characterized by strong ligand affinity and slow exchange kinetics, forms stable Cr–DNA adducts and protein–DNA crosslinks. These lesions obstruct DNA replication and transcription, impair repair pathways, and alter chromatin organization (O'Brien et al., 2003; Zhitkovich, 2011). The cumulative effect is genomic instability and persistent transcriptional dysregulation, both central drivers of chromium-induced carcinogenesis.

4.3. Metal Dyshomeostasis in Neurodegenerative Diseases

The central nervous system is particularly susceptible to metal imbalance due to its high metabolic demand, elevated oxygen consumption, and abundance of redox-active metals. Disruption of copper, zinc, or manganese homeostasis has been implicated in multiple neurodegenerative disorders (Chen et al., 2025).

Copper and Zinc

In Alzheimer's disease (AD), elevated concentrations of copper and zinc are detected within amyloid-β (Aβ) plaques. Both metals bind directly to histidine-rich regions of the Aβ peptide, promoting aggregation and stabilizing oligomeric assemblies. Copper, in particular, can undergo redox cycling in association with Aβ, generating ROS and amplifying oxidative neuronal damage (Roberts et al., 2012; Ayton et al., 2021).

Similarly, copper binding to the prion protein (PrP) influences its conformational dynamics and has been implicated in the pathogenesis of prion disorders (Millhauser, 2004). In these contexts, altered metal coordination contributes both to structural instability and to oxidative stress.

Manganese (Mn)

Chronic manganese overexposure leads to manganism, a neurotoxic condition that shares clinical features with Parkinson's disease (PD). However, the neuropathological profile differs: rather than targeting dopaminergic neurons of the substantia nigra as in PD, manganese

accumulates predominantly in the globus pallidus (O'Neal & Zheng, 2015).

Excess Mn disrupts mitochondrial function, alters dopaminergic signaling, and enhances oxidative stress, ultimately contributing to neuronal dysfunction and cell death (Harischandra et al., 2019). These findings underscore the narrow therapeutic window between essential manganese utilization and neurotoxicity.

4.4. Cobalt and Cardiovascular Toxicity

While cobalt is indispensable as the central ion of vitamin B_{12}, inorganic cobalt salts can exert systemic toxicity when present in excess. Historical cases of "cobalt cardiomyopathy" were reported in individuals consuming beer containing cobalt additives used as foam stabilizers (Packer, 2016).

More recently, systemic cobalt exposure has been observed in patients with metal-on-metal hip prostheses, where wear-induced ion release leads to elevated circulating cobalt concentrations. Such exposure has been associated with cardiomyopathy, neurological dysfunction, endocrine disturbances, and hematological abnormalities (Paustenbach et al., 2013; Grasso et al., 2024). These cases highlight the potential consequences when cobalt escapes its tightly regulated biological role within cobalamin and interacts inappropriately with cellular targets.

5. Conclusion

The interplay between transition metals and proteins exemplifies a fundamental biochemical duality: the same coordination chemistry that enables catalytic versatility and structural precision can, under dysregulated conditions, drive molecular instability and disease. Throughout this review, we have highlighted how nickel, chromium, zinc, copper, manganese, and cobalt contribute to protein folding, enzymatic catalysis, and transcriptional regulation through tightly orchestrated metalation processes.

At the structural level, metal ions shape protein energy landscapes, stabilize native conformations, and modulate folding kinetics. Functionally, their redox flexibility and Lewis acidity enable reaction pathways inaccessible to organic cofactors alone, including organometallic transformations and multielectron redox chemistry. At the regulatory level, metal binding serves as a molecular switch that links intracellular metal availability to gene expression, thereby integrating metabolic demands with environmental cues.

However, this biochemical precision depends on strict control of metal distribution, speciation, and coordination. Disruption of metal homeostasis—whether through environmental exposure, genetic defects, or age-related dysregulation—can promote mismetalation, oxidative stress, DNA damage, and proteotoxic aggregation. Such mechanisms underpin diverse pathologies, including carcinogenesis, neurodegeneration, and cardiotoxicity. Importantly, metal-induced toxicity is rarely attributable to a single pathway; rather, it emerges from the convergence of redox imbalance, structural perturbation, and regulatory interference.

Future research must move beyond isolated molecular observations toward integrative, systems-level approaches that map the dynamic interactions between the metallome and the proteome. Advances in metalloproteomics, structural biology, and metal imaging technologies will be essential for defining how cells achieve selective metalation in complex intracellular environments. A deeper mechanistic understanding of metal–protein interactions will not only clarify fundamental aspects of bioinorganic chemistry but also inform therapeutic strategies—ranging from targeted chelation and redox modulation to the exploitation of metal-dependent vulnerabilities in pathogens and cancer cells.

In this context, metal biology should not be viewed solely through the lens of toxicity or nutrition, but as a finely balanced chemical framework that underlies both cellular resilience and disease susceptibility.

Acknowledgements

We would like to express our sincere gratitude to the editorial board and the two anonymous reviewers, whose constructive suggestions greatly contributed to improving the quality of this article.

Declarations

Data and code availability

All data generated or analyzed during this study are available from the corresponding author upon reasonable request. No computational code was used in this study.

Conflicts of interest

The authors announced that they have no known conflicts of interest or personal relationships that could have appeared to influence the work reported in this manuscript.

Ethical approval

The authors declare no ethical issues; the research was carried out in full agreement with ethical standards. Also, this paper is neither under Review nor published elsewhere.

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