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Three-Dimensional Organoids in Metal Biology: Metabolism, Toxicity Assessment, and Theraputic Applications

Jiale Wen, Xinlei Fu, Haobo Liu, Xiaohong Zhang, Yongtai Xu, and Shikui Wu*

College of Pharmacy, Inner Mongolia Medical University, Hohhot 010059, China
***Corresponding Author: Shikui Wu, PhD,** College of Pharmacy, Inner Mongolia Medical University, Hohhot 010059, Inner Mongolia, China. E-mail: wushikui@immu.edu.cn

ABSTRACT

Metals have dual biological roles. Essential metals, including magnesium, zinc, and copper, are required for physiological functions within narrow homeostatic windows, whereas non-essential metals such as cadmium may exert toxic effects even at low exposure levels. Chemical form, ion, complex, or nanoparticle, further influences biological fate. However, current mechanistic understanding remains largely based on two-dimensional (2D) monolayers and animal models, both of which incompletely capture the tissue architecture and cell-cell crosstalk that govern metal behavior in vivo. Three-dimensional (3D) organoid technology has emerged as a promising approach to address this gap. This review synthesizes how intestinal, brain, kidney, liver, breast, cardiac, and tumor organoids have been used to assess metal-induced morphogenesis, metabolic reprogramming, toxicity, and therapeutic responses. We first summarize conventional findings related to metabolism, toxicity, and detoxification, and then highlight organoid-specific insights: low-dose silver nanoparticles prolong the cell cycle by impairing ciliogenesis, whereas high doses trigger apoptosis; intestinal organoids link copper handling to lipid uptake; prostate organoids reveal miR-183-regulated zinc homeostasis; and engineered nanozymes selectively scavenge reactive oxygen species in inflamed microenvironments. Critical gaps remain: most platforms lack vasculature, immune components, and systemic metabolic clearance; chronic low-dose studies are rare; and genetically diverse biobanks remain limited. Addressing these gaps is essential for transforming organoids into reliable predictive platforms for metal toxicology and drug development.

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Introduction

Metals are involved in diverse physiological processes, including catalysis, oxygen transport, signaling, and bone formation, but the boundary between physiological necessity and toxicity is narrow. Magnesium, zinc, copper, and iron are indispensable only within tightly regulated homeostatic ranges; when their concentrations fall outside these ranges, pathological conditions ranging from metabolic syndrome to neurodegeneration may occur [1-11]. Cadmium, which has no recognized physiological benefit, can damage the kidney, disrupt endocrine function, and impair development even at background exposure levels [12,13,28,29,81,88]. Further complicating this issue, chemical form strongly influences biological outcomes: chromium(III)-polysaccharide complexes show stronger glycemic regulatory effects than the corresponding ligand alone [16]; whereas silver nanoparticles disrupt multiple metabolic pathways in a manner distinct from ionic silver [21].

A major limitation is that much of the current mechanistic knowledge is derived from two conventional model systems with important limitations. Two-dimensional (2D) monolayers lack tissue architecture and paracrine signaling networks, whereas animal models are limited by species differences, low throughput, and restricted cell-type-specific resolution. When the aim is to determine cell-type- and organ-specific effects of metals, conventional models remain insufficient.

Organoids offer a promising approach to overcoming these limitations. Derived from stem cells and cultured within extracellular matrix scaffolds, they can self-organize into miniature tissues that retain structural hierarchy and functional characteristics. In recent years, intestinal, gastric, liver, kidney,

brain, breast, cardiac, and tumor organoids have been adopted in metal-related research across studies of metal homeostasis, toxicity, metabolism, and therapeutic responses [69-120].

This review is organized into two main parts. First, we summarize evidence from conventional models related to metabolism, toxicity, detoxification, and toxicity mitigation, thereby establishing the current knowledge base and the limitations that organoid models may help address. Second, we critically examine organoid-based studies, focusing on how metals affect morphogenesis, serve as targets for toxicity assessment, reveal tissue-specific metal handling and metabolic responses, and enable therapeutic evaluation. Common mechanistic themes, including mitochondrial injury, reactive oxygen species generation, DNA damage, autophagy, and cell-cycle arrest, emerge across different metals and organ systems, although each metal retains distinct biological signatures. Finally, we discuss key translational challenges, including limited vascularization, insufficient immune components, absent or incomplete clearance pathways, a bias toward acute high-dose exposure rather than chronic low-dose exposure, and a shortage of population-scale biobanks that reflect human genetic heterogeneity. Unless these challenges are addressed, organoids will remain valuable models, but not yet fully predictive platforms for metal toxicology.

2. Evidence from conventional experimental models

2.1 Metal-dependent metabolic regulation

Metal-dependent regulation of metabolism follows a dose- and form-dependent pattern. Essential metals, including magnesium, zinc, copper, and iron, support glucose metabolism, mitochondrial function, redox homeostasis, osteogenesis, hepatic metabolic function, and bone remodeling within narrow physiological ranges [1-11]. However, both deficiency and excessive accumulation can disturb metabolic homeostasis. Magnesium deficiency has been associated with impaired glucose metabolism, whereas magnesium supplementation may support osteogenesis and metabolic balance [1,2]. Copper, zinc, and iron are involved in antioxidant defense, hepatic inflammatory responses, bone remodeling, and insulin sensitivity, whereas excessive accumulation, particularly of copper or iron, may promote oxidative stress, lipid peroxidation, and inflammatory injury [5-10]. In contrast, cadmium has no recognized physiological benefit and can disrupt energy metabolism, lipid handling, pancreatic β-cell function, and gut–liver metabolic communication [12,13].

The biological effects of metals are strongly influenced by their chemical form. Metal complexes may alter metal bioavailability, enzyme inhibitory activity, antioxidant capacity, and glucose metabolism. For example, chromium(III)- polysaccharide complexes show stronger α-amylase and α-glucosidase inhibitory activity than the corresponding polysaccharides alone, suggesting that complexation can modify metabolic activity [16]. Protamine zinc insulin combined with selenium has also been reported to improve glucose metabolism in diabetic mice [17]. Metal- containing nanoparticles further complicate these effects because particle size, surface modification, dissolution behavior, and tissue distribution jointly determine metabolic outcomes. Polyethyleneimine-modified gold nanoparticles can disturb hepatic drug-metabolizing enzymes and lipid metabolism, while silver nanoparticles can affect glycolysis, the tricarboxylic acid cycle, amino acid metabolism, phospholipid metabolism, and antioxidant defense pathways [20,21].

Overall, conventional studies suggest that metal-induced metabolic effects are shaped by three interacting variables: exposure dose, chemical form, and tissue-specific metal handling [1-21]. However, most existing evidence has been derived from animal models or two-dimensional cell cultures. These systems provide limited information on how distinct cell populations within the same tissue coordinate metal uptake, storage, transport, and metabolic adaptation. This limitation provides a strong rationale for using organoid models to investigate cell-type-specific and tissue-context-dependent metal metabolism.

2.2 Shared and metal-specific toxicity mechanisms

Metal-induced toxicity often converges on several recurrent cellular stress pathways, including mitochondrial dysfunction, oxidative stress, impaired DNA repair, inflammatory signaling, cell-cycle arrest, apoptosis, autophagy dysregulation, and tissue-specific functional decline [24-29,36,38]. Manganese exposure is closely linked to neurotoxicity, mitochondrial impairment, altered mitochondrial respiration, reactive oxygen species (ROS) generation, and glial cell-mediated neuroinflammation [24,25,27]. Cadmium is associated with a broader spectrum of toxic effects, including nephrotoxicity, developmental tox-

icity, endocrine disruption, reproductive toxicity, and carcinogenic potential [28,29]. At the cellular level, cadmium can interfere with DNA repair, induce ROS production, promote apoptosis, and disrupt cell-cycle progression [28,29]. Aluminum toxicity is mainly reflected in impaired bone metabolism through disruption of collagen synthesis, bone formation, and bone remodeling [26].

Metal-containing compounds and nanoparticles exhibit additional toxicological complexity. Cisplatin, a representative platinum-based compound, induces DNA adduct formation, activates DNA damage responses, and causes tissue-dependent injury, particularly in renal and neural tissues [31,38]. Beryllium sulfate can induce apoptosis and autophagy in bronchial epithelial cells [36]. For metal-containing nanoparticles, toxicity depends not only on elemental composition but also on particle size, surface chemistry, dissolution behavior, accumulation, and target-organ distribution [39-44]. Zinc oxide nanoparticles may release zinc ions and induce cumulative toxicity, whereas nano-anatase titanium dioxide may damage the liver, kidney, and myocardium at high doses [41-43]. Silver nanoparticles may induce developmental toxicity through direct mechanisms, such as ROS generation, DNA damage, apoptosis, and cytoskeletal disruption, as well as indirect mechanisms involving maternal hormonal imbalance, inflammation, immune dysregulation, and placental impairment [44].

Taken together, metal toxicity should be considered a dynamic process shaped by dose, exposure duration, chemical form, and target-organ susceptibility [22-44]. Current evidence remains heavily weighted toward acute and/or high-dose exposure models, whereas chronic low-dose exposure, mixed-metal exposure, and long-term tissue accumulation remain insufficiently characterized. This evidence gap limits the ability of conventional models to predict outcomes under realistic human exposure scenarios.

2.3 Metal-based protective and therapeutic strategies

Metal-related intervention strategies can be broadly divided into three categories: restoration of metal homeostasis, attenuation of oxidative and/or inflammatory injury, and development of metal-containing or metal-based therapeutic materials. Magnesium supplementation has been reported to alleviate pancreatic inflammation and reduce oleic acid-induced lipid accumulation, suggesting a potential protective role in pancreatitis and fatty liver-related metabolic injury [45,46]. Zinc and selenium are closely associated with liver function, immune regulation, and antioxidant defense, and their supplementation may provide supportive benefits in advanced liver disease and related complications [48,51]. Calcium- and citrate-related interventions have also been investigated in bone metabolism and urinary calcium regulation [53,54]. Collectively, these studies suggest that correcting essential-metal imbalance may mitigate organ injury under specific pathological conditions.

Metal complexes and nanoformulations further extend metal-related intervention strategies beyond simple mineral supplementation. Chromium(III)- and zinc- containing complexes have been explored for improving glucose metabolism and insulin sensitivity [55,56]. Platinum and gold complexes have been investigated as antitumor agents, with reported mechanisms involving cytoskeletal disruption, metabolic inhibition, immune activation, and oxidative stress modulation [57,58]. Engineered nanozymes, including iron carbide nanoparticles, molybdenum-based polyoxometalate nanoclusters, ultrathin niobium carbide, and hollow MnO_2 nanoparticles, can regulate ROS levels and attenuate inflammatory or tumor-related injury in disease models [64-68]. Other metal-based nanomaterials may also exert antitumor effects by enhancing ROS generation, regulating the tumor microenvironment, or improving drug delivery [60-63,66].

Despite these promising findings, metal-based protective and therapeutic strategies remain challenging to translate directly into clinical practice. Long-term biodistribution, clearance, organ accumulation, off-target toxicity, and baseline interindividual differences in metal status remain insufficiently understood [57-68]. Therefore, more physiologically relevant models are needed to evaluate both therapeutic efficacy and potential toxicity under controlled, tissue-specific conditions. Organoids may help bridge this gap by providing human-relevant platforms for assessing metal handling, tissue repair, toxicity mitigation, and therapeutic windows in a tissue-specific context.

Table 1. Concise summary of metal-induced effects in conventional experimental models

Category	Representative examples	Main biological effects	Key mechanisms / implications
Essential metal ions	Mg, Zn, Cu, Fe	Regulate glucose metabolism, redox balance, osteogenesis, hepatic function, and bone remodeling within narrow ranges.	Deficiency or excess can disturb metabolic homeostasis, inflammation, and tissue function.
Non-essential or toxic metal ions	Cd, Mn, Al	Cause developmental, renal, neurological, reproductive, carcinogenic, or bone-related toxicity.	ROS generation, mitochondrial dysfunction, DNA repair interference, cell-cycle arrest, and impaired collagen/bone remodeling.
Metal complexes / compounds	Cr(III), Zn, cisplatin, Pt/Au complexes	Show metabolic modulation, antitumor activity, or tissue-specific toxicity depending on structure and dose.	Altered enzyme activity, DNA adduct formation, cytoskeletal disruption, immune activation, and oxidative stress modulation.
Metal-containing nanoparticles / nanozymes	GNPs, AgNPs, ZnO, TiO_2, MnO_2, POM nanoclusters	Induce metabolic disruption, developmental toxicity, ROS scavenging, or ROS-mediated antitumor effects.	Biological effects depend on size, surface chemistry, dissolution, biodistribution, and nanozyme activity.

3. Applications of Organoid Models in Metal Biology and Toxicology

3.1 Metal-dependent organoid growth and morphogenesis

3.1.1 Metal-dependent modulation of organoid growth and morphogenesis

3.1.1.1 Metal ions

Kristen et al.used gastric organoids derived from transgenic mice expressing genetically encoded calcium indicators to investigate potential sources of intracellular Ca^{2+} mobilization [69]. Voltage-gated calcium channels were found to contribute to intracellular Ca^{2+} responses during repair, suggesting that extracellular Ca^{2+} uptake contributes to calcium mobilization. In addition, store-operated calcium entry also played a critical role in calcium mobilization during recovery. Rodrigo et al. investigated nanocellulose hydrogels crosslinked with $Ca^{2+}$and Mg^{2+} as substrates for 3D cell culture, which provided the biochemical and mechanical properties required for the growth and recovery of intestinal organoids [70] . This study supports the potential use of cation-crosslinked nanocellulose hydrogels as plant-based alternative substrates in 3D cell culture systems. Durga, et al. evaluated the effects of calcium on the growth and differentiation capacity of human colonic tissue. Colonic tissue derived from histologically normal human samples retained differentiation capacity under low-calcium conditions [71] . However, a high-calcium environment induced protein remodeling that promoted cell-cell and cell-matrix adhesion, and these changes may improve barrier function and colonic tissue integrity.

Liu et al. reported that an appropriate copper concentration promoted the proliferation of ovine pancreatic ductal organoids by activating the MEK-ERK1/2 signaling pathway in a copper chaperone 1 (ATOX1)-dependent manner, whereas excessive or insufficient copper compromised organoid cell viability [72].

Rocco et al. investigated the effects of cadmium ions on human breast stem/progenitor cell-derived organoid formation [73]. They found that cadmium inhibited the proliferation and differentiation of human breast stem/progenitor cells by suppressing HIF-1a activity, thereby impairing mammosphere and breast organoid formation. A physiologically relevant dose of cadmium at 2.5 mM reduced the formation of primary mammospheres and branched organoid-like structures by 33% and 87%, respectively.

3.1.1.2 Metal compounds

Day et al. investigated the osteogenic differentiation of human mesenchymal stem cells cultured on coral hydroxyapatite/calcium carbonate scaffolds [74]. Their findings demonstrated that coral hydroxyapatite/calcium carbonate scaffolds could support

cell culture and osteogenic differentiation, suggesting their potential application as calcium-containing biomaterial scaffolds for bone tissue engineering.

DeLaForest et al. studied the role of the zinc-finger transcription factor GATA4 in gastric development [75]. GATA4 promoted the morphogenetic transition of nascent posterior foregut endoderm cells into spheroids, thereby supporting gastric organoid growth and expansion.

Strubberg et al. explored the role of the zinc-finger transcription factor PLAGL2 as a let-7-regulated target in intestinal epithelial stem cells (IESCs) [76]. They reported that PLAGL2 enhanced TCF/LEF-mediated transcriptional activity in intestinal organoids and supported the growth and survival of intestinal organoids.

Park et al. investigated gold nanoparticle brain-derived neurotrophic factor conjugates (AuNP-BDNF) in brain organoids and found that AuNP-BDNF altered the expression of 75 genes [77]. BDNF was successfully delivered into cerebral organoids through AuNP-BDNF coupling, and this coupling influenced organoid differentiation.

Han et al. showed that strain engineering of CeO_2/Mn_3O_4 nanocrystals generated highly catalytic antioxidant nanozymes that could protect the regenerative capacity of intestinal stem cells in organoid models after radiation exposure [78] . A low dose of these nanocrystals could alleviate acute radiation syndrome and improve the survival of mice exposed to lethal whole-body irradiation.

3.1.1.3 Nanoparticles

Reding et al. investigated the effects of different concentrations of niobium carbide nanosheets on intestinal organoids [79]. They found that an optimal concentration of nanosheets could stimulate intestinal organoid cells without detectable toxicity, whereas high concentrations inhibited organoid growth. Upon infrared irradiation, nanosheet-treated organoids showed enhanced viability after irradiation.

3.1.2 Metal-related injury and disease phenotypes

3.1.2.1 Metal ions

Kcnq1 encodes a pore-forming alpha subunit of a voltage-gated potassium channel. Than et al. generated Apc^{Min} mice carrying a targeted deletion of Kcnq1 [80]. They reported that Kcnq1 may function as a tumor suppressor gene, as loss of Kcnq1 increased tumor multiplicity in Apc^{Min} mice.

Xie et al. found that cadmium exposure damaged the intestinal mucosal barrier, increased inflammatory responses, markedly reduced Muc2 expression, caused loss of intestinal goblet cells, increased ROS production in mice and intestinal organoids, and overactivated Notch signaling [81]. These findings indicate that cadmium impairs intestinal barrier integrity and epithelial differentiation.

3.1.2.2 Metal compounds

Digby et al. found that cisplatin can induce acute kidney injury and preferential injury to proximal tubular cells, which may be associated with transporter expression profiles [82]. A single high dose of cisplatin induced upregulation of the proximal tubular injury marker HAVCR1, also known as KIM-1, and the inflammatory cytokine CXCL8, as well as DNA damage and cell death, thereby impairing kidney organoid viability.

Ueno et al. found that cisplatin induced partial vacuolization of tubular epithelial cells, thickening of tubular structures, and accumulation of dead-cell debris within the tubules of renal organoids [83]. In addition, electron-lucent vesicles containing organelle remnants were observed in the cytoplasm.

3.2 Organoid models for metal toxicity assessment

3.2.1metal ions

Hua et al. studied zinc-induced neurotoxicity [84]. They found that zinc exposure above 1.0 μM may induce mild neurotoxicity. These findings contribute to the understanding of biomarkers of early cerebellar development in cerebellar organoid engineering and neurotoxicity studies.

Forsythe et al. found that exposure to lead, mercury, and thallium caused a progressive decline in cardiac organoid integrity and viability, significantly decreased ATP levels or metabolic activity, and reduced beating frequency [85].

Huang et al. investigated cadmium ion-induced developmental neurotoxicity in vitro and found that cadmium ions induced neuronal apoptosis and inhibited the proliferation of neural precursor cells in cerebral organoids [86]. In addition, cadmium-treated cerebral organoids showed reduced ciliogenesis and decreased expression of cilia length-related genes, leading to transcriptional dysregulation. These findings highlight the potential neurotoxicity of cadmium to the developing brain during early embryonic development.

Ueno, et al. investigated cisplatin-induced nephrotoxicity and acute renal tubular injury [87]. They

Table 2. Representative organoid models for metal toxicity assessment

Metal / material	Organoid model	Main phenotype	Mechanistic endpoint/evidence
Cd^{2+}	Breast, intestinal, cerebral, and cardiac organoids	Impaired branching, barrier integrity, neural development, and cardiac differentiation.	HIF-1α inhibition, ROS/Notch activation, ciliogenesis impairment, apoptosis, and developmental disruption.
Cisplatin/Pt	Kidney organoids	Proximal tubular injury, reduced viability, cellular vacuolization, and degeneration.	HAVCR1 and CXCL8 upregulation, DNA damage, and cell death.
Zn^{2+}/ZnO NPs	Cerebellar and brain organoids	Mild neurotoxicity at elevated Zn exposure and cytotoxicity at high ZnO NP exposure.	Excessive intracellular Zn^{2+} accumulation and defective autophagy.
AgNPs	Cerebral organoids	Low-dose proliferation with G1/S prolongation; high-dose apoptosis.	Cilia assembly inhibition and impaired astrocyte differentiation .
Pb, Hg, Tl and other environmental toxins	Human-derived liver and cardiac organoids	Reduced organoid integrity, ATP activity, viability, and cardiac beating rate.	Functional toxicity detected by organoid viability and activity readouts.

found that cisplatin induced cell death and degenerative changes in the tubular structures of kidney organoids, including cytoplasmic vacuolization.

Wu et al. investigated the toxic mechanisms of cadmium exposure during cardiac development and found that cadmium inhibited mesoderm formation and cardiomyocyte differentiation, thereby reducing the contractile activity of cardiac organoids [88]. Cadmium also induced morphological changes and apoptosis in human embryonic stem cell-derived cardiomyocytes. These findings provide insight into the mechanisms by which cadmium exposure may contribute to congenital heart disease.

3.2.2 Metal compounds

Seiwert, et al. investigated the genotoxic and cytotoxic effects of heme iron compared with inorganic iron in mouse intestinal organoids [89]. They showed that heme iron induced ROS production and DNA damage, thereby exerting cytotoxic effects on non-malignant intestinal epithelial cells.

Guo's team reported that human urine-derived stem cells could differentiate into renal tubular epithelial cells in a kidney extracellular matrix-based three-dimensional culture system [90]. After exposure to acetone and cisplatin, CYP2E1 and KIM-1 levels were significantly increased in the three-dimensional renal culture system. These findings suggest that this three-dimensional culture system may provide an alternative platform for nephrotoxicity screening and mechanistic studies.

3.2.3 Nanoparticles

Gehad, et al. investigated the genotoxic and cytotoxic effects of heme iron compared with inorganic iron in mouse intestinal organoids [91]. They showed that heme iron induced ROS production and DNA damage, thereby exerting cytotoxic effects on non-malignant intestinal epithelial cells.

Liu et al. used 3D brain organoids to study the mechanisms of zinc oxide nanoparticle-induced neurotoxicity [92]. The experimental results showed that High concentrationentrationentrationentrationentrations of zinc oxide nanoparticles produced cytotoxicity to 3D brain organoids through autophagy defects and the accumulation of zinc ions in cells.

Huang's research investigated silver nanoparticle-induced developmental neurotoxicity and found that silver nanoparticles interfered with the growth of cerebral organoids in a concentration-dependent manner and induced apoptosis [93]. Low concentrations of AgNPs (0.1 μg/mL) impaired ciliary assembly, thereby prolonging the G1 and S phases of the cell cycle, which was associated with increased cell proliferation in cerebral organoids. In contrast, high concentrations of AgNPs (0.5 μg/mL) inhibited astrocytic differentiation, thereby promoting neuronal apoptosis.

3.3 Organoids for tissue-specific metal metabolism

3.3.1metal ions

Stewart et al. evaluated intracellular Ca^{2+} responses in mouse mammary epithelial cells using

three distinct model systems to compare model-specific pharmacological responses [94]. They found that primary cells cultured in two-dimensional (2D) conditions and three-dimensional (3D) mammary organoids exhibited broadly similar Ca^{2+} responses to multiple stimuli, whereas immortalized mammary epithelial cells showed distinct response profiles.

KCNJ11 encodes Kir6.2, a major pore-forming subunit of the ATP-sensitive potassium (KATP) channel. Dalgin et al. investigated cerebral organoids carrying the KCNJ11 p.Val59Met (V59M) mutation [95]. The mutant cerebral organoids showed a marked reduction in neurons localized to upper cortical layer-like structures. Continuous treatment with the KATP channel blocker tolbutamide partially rescued the neurodevelopmental abnormalities.

Pierson et al. used intestinal epithelial organoids to investigate the metabolic relationship between intestinal copper uptake and lipid absorption [96]. Intestinal organoid-derived epithelial monolayers provided a useful platform for investigating the epithelial transport and metabolism of specific nutrients and compounds.

Dambal et al. found that physiologically relevant expression of the miR-183 family regulates zinc homeostasis and oncogenic pathways in prostate epithelial cells [97]. Overexpression of the miR-183 cluster reduced zinc transporter expression and intracellular zinc levels in primary prostate epithelial organoids.

Ahmad et al. investigated how the abundance of 12α-hydroxylated bile acids (12αHBAs) in the bile acid pool regulates intestinal manganese transport [98]. They found that a low abundance of 12αHBAs in the bile acid pool promoted cellular manganese efflux. Bile acid pool-dependent induction of the manganese efflux transporter SLC30A10 was primarily driven by cholic acid-mediated vitamin D receptor signaling. Administration of cholic acid or vitamin D receptor agonists increased Slc30a10 expression in the mouse ileal epithelium.

3.3.2 Metal compounds

Dvorák et al. reported that the human pregnane X receptor (PXR) is an important regulator of xenobiotic and drug metabolism and plays important roles in maintaining intestinal homeostasis and regulating inflammatory responses [99]. The lead compound FKK6 was shown to bind directly to PXR in solution and to attenuate intestinal inflammation by reducing pro-inflammatory cytokine-associated cellular responses. These findings suggest that the development of microbial metabolite mimetics may represent a feasible strategy for drug discovery.

Wang et al. found that fibrillin-1 (FBN1) expression was significantly elevated in cisplatin-resistant ovarian cancer organoids and tumor tissues, suggesting that FBN1 may be a key mediator of chemoresistance in ovarian cancer [100]. FBN1 was associated with cellular adaptation to metabolic stress and promoted angiogenic activity in vitro and in vivo. It also contributed to ovarian cancer cell chemoresistance through its involvement in glycolytic regulation and angiogenesis. These findings identify FBN1 as a potential therapeutic target for overcoming cisplatin resistance in ovarian cancer.

3.3.3 Nanoparticles

Sokolova et al. investigated nanoparticle penetration and cellular uptake in multicellular tumor spheroids [101] . They found that nanoparticles penetrated into the spheroid core, whereas free molecules, including fluorescent dyes, showed substantially less efficient penetration. Compared with larger nanoparticles, ultrasmall nanoparticles penetrated nonvascularized tumor tissue more effectively. Their cellular uptake occurred through multiple endocytic pathways, which may facilitate efficient cellular internalization.

3.4 Organoids for evaluating metal-based therapies

3.4.1 Tumor

Cristiano et al. developed DNA-based polymeric films loaded with aluminum chloride phthalocyanine (AlClPc) as a photosensitizer for early-stage breast cancer photodiagnosis and photodynamic therapy [102]. MCF-7-derived three-dimensional (3D) tumor spheroids were used to model key features of the tumor microenvironment. Following photoactivation, MCF-7 cell viability decreased in a light fluence- dependent manner, with an approximately 50% reduction in the 3D tumor spheroids at the highest tested light fluence of 1800 mJ/cm^{-2}.

Vaden et al. demonstrated that the natural-product mimic zinaamidole A (ZNA) selectively promoted cellular Zn^{2+} uptake in transformed cells, thereby inducing cancer-selective cell death [103]. Its selectivity was further evaluated using 3D organoid models derived from normal and transformed mouse mammary glands, supporting the potential of ZNA as a cancer-selective zinc ionophore.

Asahina investigated the effects of zinc chelators on pancreatic tumor organoids [104]. Treatment with

the zinc chelator TPEN caused organoid degeneration, which was rescued by zinc supplementation, indicating that zinc was required for tumor organoid growth and survival. In contrast, TSQ alone did not substantially affect organoid growth, whereas combined treatment with TSQ and zinc induced strong TSQ-zinc complex formation, organoid degeneration, and cell death. These findings suggest that dysregulated intracellular zinc homeostasis, particularly TSQ-zinc complex formation under zinc-overload conditions, may represent a therapeutic vulnerability in pancreatic tumors.

Liu et al. found that the zinc transporter ZIP4 promoted pancreatic cancer cell plasticity, interactions with the extracellular matrix, organoid development, and epithelial-mesenchymal transition (EMT) [105] . These findings suggest that ZIP4 may represent a potential therapeutic target for pancreatic cancer.

Xiao et al. investigated a heteroleptic gold(I)–bis-N-heterocyclic carbene (bis-NHC) complex [106]. Its biphenyl moiety was proposed to enhance cellular membrane penetration, thereby improving its in vitro antiproliferative activity. The complex induced mitochondrial dysfunction and apoptosis, accompanied by suppression of Nrf2 signaling and TrxR activity or expression, and exhibited potent antitumor activity against endometrial cancer cells.

Chen et al. found that mesoporous silica-coated gold nanorods exerted antitumor effects against neuroendocrine tumors (NETs) under near-infrared irradiation [107]. In vitro, cell viability decreased significantly in an irradiation time-dependent manner. In vivo, the tumor surface temperature increased rapidly following irradiation, whereas no evident inflammatory lesions or tissue necrosis were observed in major organs under the reported experimental conditions. These findings support further investigation of this nanoplatform for the treatment of NETs.

Ye et al. found that treatment under mildly acidic conditions (pH 6.5), corresponding to combined starvation therapy and chemodynamic therapy (ST/CDT), or under laser irradiation, corresponding to combined starvation and photothermal therapy (ST/PTT), significantly enhanced cytotoxic efficacy [108]. Cell viability decreased to 48.1% and 19.6%, respectively. The upregulation of gene sets associated with glucose deprivation, oxidative stress, and heat-stress responses supported the proposed mechanisms underlying the observed therapeutic effects of the gold nanoparticle-based platform.

Pucelik et al. investigated the antitumor activity of silver nanoparticles and found that the cytotoxicity and tumor selectivity of AgNPs in colon organoids were associated with increased apoptosis in cancer cells and reduced DNA synthesis [110].

Lu et al.investigated the antimetastatic activity of fructose-functionalized micelles carrying the ruthenium(II) complex RAPTA-C [111]. The micellar formulation significantly enhanced cellular uptake of ruthenium. RAPTA-C inhibited ovarian cancer cell invasion in an omental model in both its free and micelle-loaded forms. These findings support further preclinical evaluation of this nanomedicine for the treatment of metastatic ovarian cancer.

3.4.2 Cardiovascular and Cerebrovascular Systems

Alessandra et al.investigated the effects of magnesium salts on human brain organoids cultured in the presence or absence of an in vitro blood-brain barrier (BBB) [112]. They found that 5 mM magnesium pidolate (MgPid) was more effective than $MgSO_4$ in increasing the expression levels of γ-aminobutyric acid (GABA) receptors and brain-derived neurotrophic factor (BDNF), while reducing N-methyl-D-aspartate receptor (NMDAR) expression, particularly in brain organoids cultured with the BBB model. These findings provide insight into the potential mechanisms underlying the neuroprotective effects of magnesium.

Sudhahar et al. used vascular tissues from mouse models of type 1 diabetes mellitus (T1DM), vascular smooth muscle cells, and ex vivo vascular cultures to investigate the role of copper homeostasis in endothelial function [113]. They demonstrated that the copper transporter ATP7A maintained extracellular superoxide dismutase (SOD3) activity, thereby reducing extracellular superoxide ($O_2^{\bullet}$) levels, increasing nitric oxide (NO) bioavailability, and preserving endothelial function. These findings identify ATP7A as a potential therapeutic target for oxidative stress-related cardiovascular and metabolic disorders.

3.4.3 nervous system

Sun et al. used human neurons and cerebral organoids to investigate neuronal hyperexcitability in Angelman syndrome [114]. They demonstrated that ubiquitin-protein ligase E3A (UBE3A) suppresses neuronal hyperexcitability through ubiquitin-mediated degradation of large-conductance calcium- and voltage-activated potassium (BK) channels. Loss of UBE3A increased BK-channel activity, resulting in

Table 3. Organoid applications in metal metabolism and metal-based therapy

Application focus	Metal / material	Organoid model	Key insight
Metal transport and metabolism	Cu^{2+} / ATP7B-related copper handling	Intestinal organoids	Copper homeostasis is linked to lipid absorption and may contribute to gastrointestinal manifestations of Wilson disease .
Zinc homeostasis	Zn^{2+} / miR-183 family	Prostate organoids	miR-183 overexpression reduces zinc transporter expression and intracellular zinc levels .
Bile acid–manganese interaction	Mn / Slc30a10 transporter	Intestinal models	Bile acid composition regulates Slc30a10 expression and manganese efflux.
Chemoresistance	Cisplatin / FBN1 axis	Ovarian cancer organoids	FBN1 promotes glycolysis and angiogenesis, contributing to cisplatin resistance.
Metal-based antitumor therapy	Gold, silver, ruthenium, and related formulations	Tumor spheroids / organoids	Metal-based agents reduce tumor viability, promote apoptosis, or inhibit invasion depending on formulation and exposure conditions .
Barrier and inflammatory responses	Multi-mineral products and engineered nanoparticles	Intestinal organoids / gut-related models	Mineral supplementation and engineered nanoparticles can modulate barrier proteins, inflammation, and intestinal homeostasis.

enhanced intrinsic neuronal excitability and network synchronization. BK-channel antagonists normalized neuronal excitability in human and mouse neurons and ameliorated seizure susceptibility in a mouse model of Angelman syndrome. These findings suggest that BK channelopathy contributes to epilepsy in Angelman syndrome.

3.4.4 Gastrointestinal system

Aquamin® is a natural multimineral product rich in calcium and magnesium and containing multiple trace minerals. Muhammad et al. evaluated its effects using three-dimensional (3D) colonic organoid cultures derived from individuals with ulcerative colitis [115]. Aquamin® increased the expression of multiple proteins involved in colonic epithelial barrier formation and maintenance, suggesting that this multimineral intervention may support epithelial barrier function in ulcerative colitis.

Federico et al. found that, under iron-deficient conditions in intestinal organoids, inactivation of NCOA4 impaired intestinal epithelial regeneration [116]. This effect was accompanied by increased DNA damage, reduced cell proliferation, and increased cell death.

Pierson et al. used intestinal organoids derived from Atp7b-knockout mice to generate three-dimensional intestinal tissue models [117]. They found that copper homeostasis was closely associated with lipid metabolic pathways and suggested that disrupted copper and lipid homeostasis in intestinal epithelial cells may contribute to the gastrointestinal manifestations of Wilson disease.

Sauer et al. used three-dimensional (3D) intestinal organoids cultured under zinc-restricted conditions to investigate the effects of zinc deficiency on intestinal epithelial integrity and inflammatory responses [118]. They found that zinc-restricted conditions impaired intestinal epithelial barrier integrity and activated pro- inflammatory signaling pathways. When considered together with complementary microbiota-related evidence, these findings suggest that zinc deficiency may also be associated with alterations in gut microbiota composition that further exacerbate intestinal inflammation.

Nag et al. investigated the protective and antitumor effects of auranofin in models of gastrointestinal injury and abdominal malignancy [119]. Auranofin was reported to interfere with the ubiquitin-proteasome system, thereby attenuating treatment-induced cytotoxicity. It also induced reversible p53/p21-mediated cell-cycle arrest, which was associated with reduced radiation-induced injury and improved survival. In malignant models, auranofin inhibited tu-

mor growth by disrupting proteasomal protein degradation and inducing endoplasmic reticulum stress, the unfolded protein response, and apoptosis. These findings support further evaluation of auranofin as an adjunctive therapeutic strategy for abdominal malignancies.

Guilloteau et al. investigated the effects of engineered nanoparticles (ENPs) on intestinal homeostasis [120]. They reported that several commonly encountered ENPs, including Ag, TiO_2, Ti, and SiO_2 nanoparticles, may disrupt intestinal homeostasis by directly altering cytokine expression in intestinal epithelial cells. Following inhalation exposure, these nanoparticles may also modulate intestinal inflammatory responses and gut microbiota composition.

3.5 Advantages

Compared with conventional two-dimensional (2D) cultures, organoids more effectively preserve tissue architecture, multicellular organization, epithelial polarity, lineage-specific differentiation, and cell-cell and cell-matrix interactions. These features are particularly important for metal toxicology because metal uptake, storage, efflux, and toxicity are often cell-type-specific and influenced by the local tissue microenvironment. For example, gastric, intestinal, pancreatic, and breast organoid models have been used to investigate intracellular Ca^{2+} mobilization, the compatibility of Ca^{2+}- and Mg^{2+}-crosslinked culture matrices, calcium-dependent epithelial differentiation, copper-dependent regulation of organoid growth, cadmium-induced impairment of mammary organoid formation, and disruption of intestinal epithelial differentiation and barrier integrity [69-73,81]. Cerebral organoids provide a platform for assessing metal-induced developmental neurotoxicity, including zinc-induced neurotoxicity, cadmium-induced neuronal apoptosis, impaired neural precursor-cell proliferation and defective ciliogenesis, zinc oxide nanoparticle-induced autophagic dysfunction, and silver nanoparticle-induced ciliary disruption and apoptosis [84,86,92,93]. Kidney and cardiac organoids further enable the assessment of cisplatin-induced renal tubular injury and cadmium-induced impairment of cardiac development, which are less readily modeled using simple monolayer cultures [82,83,87,88].

Organoids also offer several advantages over animal models in specific experimental contexts. They can be generated from human stem cells or patient-derived tissues, thereby minimizing the influence of species-related differences in metal transporters, metabolic enzymes, stress-response pathways, and developmental programs. Human-derived cardiac organoids have been applied to the assessment of environmental metal toxicity, whereas kidney organoids and urine-derived three-dimensional renal tubular models have been used for nephrotoxicity assessment [85-90]. In addition, organoid systems are compatible with live-cell imaging, molecular profiling, dose–response testing, and targeted genetic or pharmacological perturbation. These characteristics make organoids useful platforms for identifying early toxicity biomarkers, comparing the biological effects of different metal forms, and evaluating tissue-specific therapeutic windows [84-93].

3.6 Limitations

Despite these advantages, current organoid models retain several important limitations. Most conventional organoid systems lack mature vasculature, functional immune components, innervation, and systemic processes governing metabolism and clearance. These deficiencies may limit accurate modeling of metal distribution, tissue exposure, inflammatory responses, and long-term accumulation. In addition, many current studies rely on short-term exposure to relatively high metal concentrations, whereas real-world environmental and occupational exposures commonly occur at low levels over prolonged periods. Another major limitation is the incomplete maturation of several organoid systems, particularly cerebral, cardiac, and renal organoids, which may limit their ability to recapitulate responses characteristic of mature adult tissues [82-88,92,93]. Therefore, findings obtained from organoid models should be interpreted in conjunction with toxicokinetic or pharmacokinetic data, animal studies, and clinical or epidemiological exposure evidence.

3.7 Standardization and future directions

Future organoid-based metal toxicity studies should adopt standardized and transparent experimental designs. Key parameters should include metal identity, oxidation state, chemical form, particle size and surface chemistry of nanoparticles, exposure concentration and duration, culture matrix, organoid maturation stage, endpoint selection, and data-normalization methods. Toxicity assessment should integrate morphological evaluation with quantitative functional and molecular readouts, including viability, ATP content or ATP-based metabolic activity,

Table 4. Recommended reporting checklist for organoid-based metal toxicity studies

Reporting domain	Minimum information to report	Purpose
Metal / material characterization	Element, chemical form, oxidation state, concentration, purity, particle size, surface chemistry, dissolution, aggregation, and sedimentation.	Enables comparison across ions, complexes, and nanoparticles.
Organoid model	Species or donor source, organoid type, culture matrix, passage number, maturation stage, and differentiation markers.	Defines model relevance and reproducibility.
Exposure design	Dose range, exposure duration, route of administration, acute or chronic exposure setting, and control groups.	Supports dose–response interpretation and translational relevance.
Toxicity endpoints	Morphology, viability, ATP production, ROS, mitochondrial function, DNA damage, apoptosis, autophagy, barrier integrity, and lineage markers.	Captures both phenotypic and mechanistic toxicity.
Data interpretation	Normalization method, replicate strategy, statistical approach, and integration with animal, pharmacokinetic, or clinical evidence.	Improves reliability and cross-study comparability.

reactive oxygen species generation, mitochondrial function, DNA damage, apoptosis, autophagy, barrier integrity, lineage-specific markers, and transcriptomic and/or metabolomic profiling. These endpoints have been applied in varying combinations in studies of cadmium, cisplatin, zinc oxide nanoparticles, silver nanoparticles, and other metal-containing materials using cerebral, renal, intestinal, cardiac, tumor, and related three-dimensional organoid systems [81-93,101-120]. For nanoparticles, dissolution, aggregation, sedimentation, and intracellular localization should also be reported because nanoparticle behavior can substantially influence penetration into three-dimensional tissues, cellular uptake, and toxicological outcomes [91-93]. Establishing standardized reporting criteria will improve reproducibility and facilitate meaningful comparisons across organoid types, metal classes, and exposure models.

Overall, organoids should not be regarded as complete substitutes for animal studies or clinical investigations, but rather as complementary, human-relevant platforms that can refine mechanistic understanding, enhance early-stage toxicity screening, and support the development of safer metal-based therapeutic strategies [102-120]. Their predictive value could be further improved through enhanced organoid maturation, incorporation of vascular and immune components, standardized chronic low-dose exposure protocols, and the establishment of genetically diverse organoid biobanks.

4. Conclusion and future perspectives

Metals have dual and context-dependent roles in biological systems. Essential metals are required within tightly regulated homeostatic ranges, whereas non-essential metals may exert toxic effects even at relatively low exposure levels. The first major part of this review summarized how metal ions, complexes, and nanoparticles influence metabolic processes and organ injury in conventional experimental models. Common mechanisms included disruption of metal homeostasis, mitochondrial dysfunction, oxidative stress, impaired DNA repair, and inflammatory injury, although their relative importance varied among metals and chemical forms. The biological effects of metal-containing nanoformulations were further influenced by physicochemical properties such as particle size and surface chemistry. Nevertheless, much of the available evidence has been derived from two-dimensional cultures or whole-animal models, which provide limited resolution of cell-type-specific metal handling and tissue responses.

Organoid models have emerged to address this limitation. As outlined in the second section, 3D cultures of intestinal, cerebral, renal, and tumor tissues have uncovered metal-dependent effects on tissue morphogenesis and structural integrity: calcium and magnesium promote epithelial barrier formation, cadmium disrupts tissue branching architectures, and copper modulates growth dynamics *via* ATOX1-ERK signaling. Toxicity profiling in organoids has also uncovered concentration-dependent phenotyp-

ic shifts: low-dose silver nanoparticles slow cell cycle progression by impairing cilia assembly, whereas high doses trigger apoptosis by blocking astrocyte differentiation. Such nuanced effects are readily missed in conventional, simplified culture systems. Further metabolic investigations using organoids have clarified interactions between copper and lipid metabolism, zinc and microRNA regulation, as well as bile acid profiles and manganese efflux, intercellular crosstalk that more closely mirrors the in vivo cellular microenvironment.

Organoid models have emerged as promising platforms for addressing the limited tissue and cell-type resolution of conventional experimental systems. Intestinal, cerebral, renal, mammary, pancreatic, and tumor organoids have revealed metal-dependent alterations in morphogenesis, epithelial differentiation, barrier integrity, and tissue-specific growth. They have also captured concentration- dependent toxicity that may be difficult to resolve in monolayer cultures. For example, low-concentration silver nanoparticles altered ciliary assembly and cell-cycle progression, whereas higher concentrations inhibited astrocytic differentiation and promoted neuronal apoptosis. Organoid studies have further clarified tissue-specific relationships between copper and lipid metabolism, miR-183-mediated zinc homeostasis, and bile acid-regulated manganese efflux. Collectively, these findings demonstrate the value of organoids for resolving metal responses within a physiologically relevant tissue context.

Future studies should incorporate vascularization strategies, functional immune components, chronic low-dose exposure paradigms, and genetically diverse organoid biobanks to enhance the translational relevance and predictive performance of organoid-based metal toxicity models.

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