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Review Article

Cadmium-induced Alterations in the Expression Profile of MicroRNAs: A Comprehensive Review

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Abstract

Environmental factors such as heavy metals can influence the gene expression profiles that can lead to diseases. MicroRNAs (miRNAs) are primary regulatory molecules related to health and disease that are sensitive to environmental factors. Several studies have shown an association between environmental exposure to toxic metals such as cadmium (Cd) and disease risk. Growing knowledge has shown that heavy metal toxicity can manifest through miRNAs. Therefore, dysregulated miRNAs are proposed as potential biomarkers for monitoring chronic metal exposure. This review aimed to evaluate the effect of Cd on changes in miRNA expression. The databases of PubMed, Web of Science (ISI), Scopus, and Google Scholar were systematically searched for all previous relevant articles from 2000 up to 2022. The following medical subject headings were used: (microRNAs OR miRs) AND (Heavy Metals OR Cadmium OR Cd) AND (miRs profile OR miRs Expression). Searched articles were divided into the categories of *in vitro*, *in vivo*, and human studies. MiRNAs, widely used for biomarker discovery in Cd-induced diseases, are still being researched to use these genes for reliable biomarker discovery in addition to current diagnostic and prognostic approaches. As the functional effects of miRNAs are by their target proteins, it is important to analyze the expression levels of multiple potential target proteins to fully understand the role and mechanism of miRNAs in Cd-induced diseases. Therefore, further investigations are required to understand the regulatory mechanisms of miRNAs and to obtain novel biomarkers, and these findings will be used to develop early diagnostic approaches as well as new preventive methods and treatment options for Cd-induced diseases.

Introduction

The interaction between genes and environmental agents can lead to the progression of several diseases.[1] MicroRNAs (miRNAs or miRs), as the main regulatory factors in health and disease states, have been reported to respond to various environmental exposures.[2,3] These findings highlight the effect of heavy and toxic metals on the function of human miRNAs and the development of diseases such as various types of human cancers as well as metabolic and neurological disorders. Because metals exist naturally in the Earth's crust and are used in industry, they are a large class of pollutants that are spread throughout the world. Epidemiological and experimental studies have shown a relationship between an increased risk of disease and long-standing exposure to heavy metals, including cadmium (Cd), arsenic (As), and lead (Pb).[4,5] These metals tend to congregate in certain tissues of the human body and are considered a potential threat to human health.[6] The function of heavy metals in disease development and progression depends on the genetic background as well as on the amount and duration of exposure. The molecular mechanisms involved in heavy metal-related diseases are well understood, including identified interactions with proteins, DNA damage, enhanced DNA replication and cell cycle, reactive oxygen species production, and epigenetic vari-

Keywords: MicroRNAs; miRNAs, Gene expression profiling; Toxic metals; Cadmium; Human diseases.

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ations.[7] Most studies have demonstrated this association by measuring messenger RNA expression. However, recent experimental data indicate the altered expression of miRNAs upon exposure to Cd, Pb, As, and other metals.[8] MiRNAs consist of a big family of noncoding and single-stranded RNA that play a major role in the regulation of gene expression at the post-transcriptional level, which can lead to translational degradation or repression of the target gene. According to research, miRNAs are very important for the normal functioning of the body and participate in various biological processes, and their aberrant expression is related to several diseases in humans. In addition, miRNAs are also secreted into the extracellular biological fluids, and their extracellular variants also have been broadly described as potential diagnostic biomarkers for several disorders and act as signaling molecules for cellular communication.[9,10] Accordingly, dysregulated miRNAs identified in patients affected by several diseases may serve as biomarkers for the early diagnosis and evaluation of disease progression. This review markedly emphasizes the effects of toxic heavy metals on human miRNA activities and how this contributes to the progression of various diseases. Herein, we summarize the recent experimental data on alterations of miRNA expression induced by Cd.

This study provides a comprehensive review to identify and list altered miRNAs induced by the heavy metal Cd, which are associated with the industrialization of societies and diseases caused by heavy metal pollution. All of the *in vitro*, *in vivo*, and clinically available studies related to this topic were collected through searches of electronic databases, including PubMed, Web of Science (ISI), Scopus, and Google Scholar. The following terms were applied to gather relevant studies (microRNAs OR miRs) AND (Heavy Metals OR Cadmium OR Cd) AND (miRs profile OR miRs Expression). Only English-language literature publications were included in this narrative review. This review focuses on the recent studies showing Cd-induced miRNA dysregulation and the underlying mechanisms in the development of diseases such as cancer. We expect that these data will provide a meaningful resource for understanding the global transcriptional responses to Cd and how they are modulated by miRNAs.

Toxic metals and diseases

Generally, metals are categorized into two groups: essential (important for life) and nonessential (without known functions to humans). In trace amounts, some heavy metals are essential for optimal health, while exposure to nonessential metals presents the potential hazards of acute and chronic organ toxicity.[11] For instance, excessive amounts of metals in various organs can cause cellular events such as oxidative stress, mitochondrial and genomic disorders, protein folding disorders, and apoptosis-inducing activation.[12] Cd, Pb, and mercury are three primary heavy metals listed by the World Health Organization as the top 10 toxic metals of main public health concern. These metals not only play an effective role in human biological activity but also cause different toxic effects on humans and other organisms. Heavy metals, including Cd, As, Pb, mercury, and manganese are biological pollutants that cause various kidney diseases and cancer as well as inhibit the growth of children. In addition, manganese is known as an essential cofactor for some enzymatic pathways that drive biological functions. Moreover, it is a potential source of neurotoxicity, especially in the field of movement disorders.[13]

Heavy metals on the surface of the Earth can enter the human body via breathing and absorption through the skin; when they accumulate in various tissues, they can cause disorders of the body's immune system and disturbances in cell metabolism.[14] Although these metals are found naturally in the soil, their concentration in the soil, air, and water has increased as a result of human activities and the industrial and economic growth of societies; therefore, they have exceeded the natural limit, which is harmful to the environment. They are also dangerous for humans. Once these elements enter the environment, they cannot be eradicated, but they change chemically and their bioavailability and toxicity change; eventually, they can pollute the food cycle, water, air, and soil.[15] One of the important challenges related to heavy metals is that they cannot be metabolized in the body. When these metals enter the body, they accumulate in tissues like bones, adipose tissue, muscles, and joints, and this accumulation causes many diseases in humans. In this regard, heavy metals are usually excreted extremely slowly from the body. For instance, Cd has a half-life in the blood of 3–4 months, making this choice helpful for recent exposure. However, Cd has a remarkably high half-life of almost 30 years in the body.[16] Other metals including As and Pb have a half-life of about 3–4 h and 1–2 months in the blood, respectively.[17] The effects of heavy metal entrance on the body can include all kinds of cancers, respiratory diseases, cardiovascular disorders, liver and kidney complications, arthritis, osteoporosis, hormonal problems, etc. Cd is a heavy metal element and is very toxic. This is because it has no biological role in the body and poses a threat to human health. The International Agency for Research on Cancer has described Cd, which has no known physiological function, as a significant warning to human health.[18] Although Cd is distributed naturally, its concentration in the environment is elevated because of smelting, cooking, and pigments. There is also food and water in the air. The World Health Organization has announced that Cd is among the 10 chemicals that are toxic to human health.[19] This metal has a toxic effect on the liver, renal system, cardiovascular system, and reproductive systems through various mechanisms. The most common mechanisms of heavy metal toxicity are oxidative stress and interactions with body proteins and enzymes, as well as changes in miRNA expression.[20] In recent years, associations between Cd and changes in miRNA expression have been reported. The effects of environmental metallotoxins on the epigenome have attracted increasing attention among researchers in recent years. Epigenetically modified gene expression by variations in the chemical composition of associated nucleotides or histones, rather than through changes in the genome sequence, can occur. Three common changes have been investigated, including methylation of genetic material, modification of histones, and expression of noncoding RNAs such as miRNAs.[7] Considering the influence of heavy metals on the expression levels of miRNAs, which play a fundamental role in human-related diseases, we aimed to review and analyze published data on Cd-responsive miRNAs (as potential biomarkers) and collect data on changes in the expression of miRNAs. The toxic roles of Cd exposure on the different organs of humans are summarized in Figure 1.

Overview of the biogenesis and mechanism of action of miRNAs

With the increase in biological investigation and the development of advanced approaches, miRNAs have received increasing attention. In this regard, several studies have shown a connection between miRNAs and the development of various diseases. In general, miRNAs are a group of endogenous, relatively small, noncoding, single-stranded RNAs of approximately 19–22 oligonucleotides with essential roles in gene expression at the post-

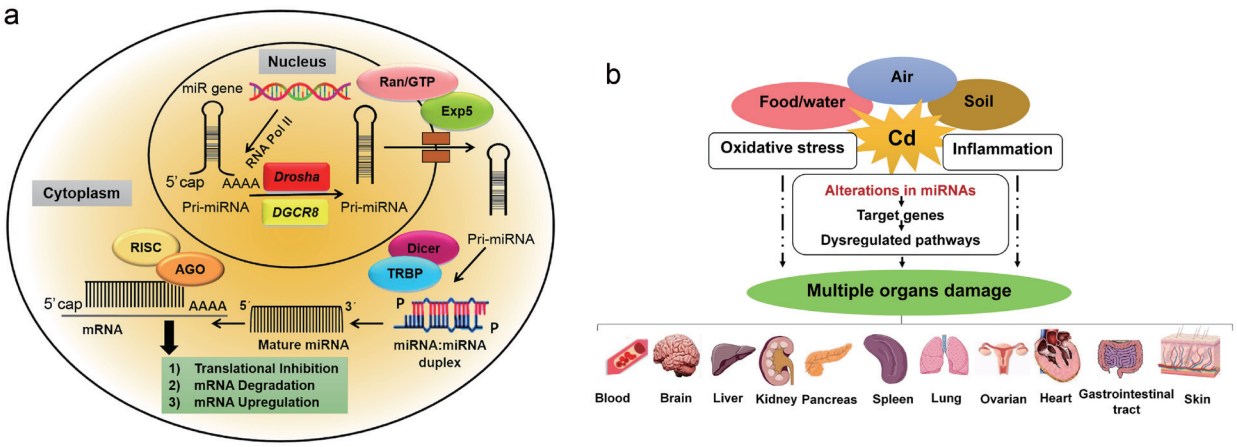

Fig. 1. The miRNA biogenesis and toxic roles of Cd on the different organs of human. (a) General diagram of the miRNA biogenesis pathway. (b) The major routes of cadmium exposure and its toxic impacts. AGO, Argonaute; Cd, cadmium; Exp5, Exportin 5; miRNA, microRNA; Ran/GTP, Ras-related Nuclear protein/Guanosine Triphosphate; RISC, RNA-induced silencing complex; TRBP, TAR RNA-binding protein.

transcriptional level.[21] Since miRNAs were discovered about two decades ago, scientists have identified thousands of miRNAs from different species. Human miRNAs act in pairs with a complementary sequence in messenger RNA. Most of them are transcribed from DNA into primary miRNAs; after processing, they are converted into precursor miRNAs and then mature miRNAs. Often, miRNA interacts with the 3′-untranslated region of the target messenger RNA to repress gene expression. In addition, it is reported that miRNAs can interact with the 5′-untranslated region, coding sequence, and promoters of genes.[22] On the other hand, miRNAs have been described to activate the expression of genes under specific conditions.[23] Both the sequence and the structure of miRNAs determine their function. As a result, these molecules can play a role in very well-known cellular processes, depending on their sequence. Taken together, the unique characteristics encoded in the sequence and the structure of mature miRNA can be an important sign to understand the function of miRNAs. Thus, it has been concluded that even closely related miRNAs in terms of structure have different functions across species.[24] Recently, studies have shown that miRNAs shuttle between various intracellular compartments to control the gene translation and transcription rate.[9] miRNAs are important to the normal growth of organisms and participate in various biological processes,[25–27] and abnormal expression of this class of RNA results in different diseases.[28–30] In addition, according to studies, miRNAs are also released into extracellular biofluids, which have been broadly reported as potential biomarkers of diseases and also as signaling molecules in cellular connections.[31] The biogenesis of miRNAs begins with the processing of the resulting transcripts by RNA polymerase II/III.[21] Sometimes, miRNAs are transcribed into a long transcript called a cluster that might contain similar parts, in which case they are considered a family.[32] The biosynthesis of miRNAs takes place by two canonical and noncanonical pathways.[31] The canonical biogenesis pathway is the predominant pathway through which miRNAs are processed. In this way, primary miRNAs are transcribed from their genes and then processed into precursor miRNAs by a microprocessor complex consisting of DGCR8 and the ribonuclease III enzyme Drosha.[33] The precursor miRNA is then moved to the cytoplasm through an exportin 5/Ran-guanosine-5′-triphosphate-dependent manner and processed to generate the mature duplex miRNA.[34] Finally, the 5P or 3P strands of the mature duplex miRNA are loaded onto the Argonaute family of proteins to form the miRNA-induced silencing complex.[35] A general outline of miRNA biogenesis is shown in Figure 1. Currently, more than 17,000 different mature miRNAs have been discovered from more than 142 species.[36] Examination of different species has shown that many miRNAs are extremely conserved between species. This protection indicates that this class of molecules is involved in important biological functions, including the regulation of gene expression at the transcriptional and translational levels, which are key events in cellular homeostasis.[37] Right now, it is clear that environmental agents, such as toxic metals, can affect the function and expression of miRNAs. The extent of miRNA expression changes also depends on the type of toxicant to which the cells are exposed.[38] For instance, it has been reported that the expression of miR-146α is reduced after exposure to Cd, but its expression is increased when exposed to aluminum.[39] Research results have indicated that miRNAs have important effects on early cell growth, the proliferative power of cells, cell differentiation, developmental processes, the aging process, and apoptosis pathway 3 as well as in the pathogenesis of diseases. For instance, miR-7α has clinical importance in gastric cancer.[40] In addition, miRNAs may participate in the development of neurological diseases such as Alzheimer's disease and Parkinson's disease in response to exposure to toxins by stimulating oxidative stress or inflammation.[40,41]

Overview of Cd-induced changes in miRNA expression

Xenobiotics, chemical compounds, are foreign to the organism or ecosystem and are constantly detected in the environment. As the amount of chemicals synthesized increases, all these compounds eventually end up in the environment and pose a threat to all shapes of life, from microbes to humans. When they enter into biological systems, they affect the body's homeostasis, causing various adverse genetic changes. Gene expression upon exposure to these compounds is regulated by an epigenetic mechanism,[23] which regulates gene expression at both the transcriptional and translational levels. Research on miRNAs' interaction with environmental toxins is expanding due to their growing importance. A lot of research has been done in this area. For example, using a plant model, Jian *et al*. have shown that exposure to Cd for three days caused changes in the expression of 39 miRNAs involved in

homeostatic functions, stress responses, transcription factor regulation, and secondary metabolic responses of cells.[42] Therefore, consumption of contaminated plants leads to higher Cd concentrations and bioaccumulation. Therefore, the identification of regulatory miRNAs may lead to reduced Cd accumulation and reduced toxicity associated with Cd absorption. In addition, another study has investigated whether miRNAs function in response to Cd stress and examined miRNA expression in rice under Cd stress by using a microarray approach.[43] A total of 12 miRNAs were identified in response to Cd, four of which were experimentally confirmed. In addition, target genes of miRNAs identified in response to Cd were predicted, most of which appear to regulate gene networks mediating environmental stress. Moreover, a transgenic procedure was also used to evaluate the role of miRNAs in rice response to Cd. The upregulation of miR-192 delayed seed germination and seedling growth under Cd exposure. These data indicate the role of miRNAs in the tolerance of rice plants to Cd toxicity.[43] In the field of investigating miRNA expression changes after Cd exposure, several studies have been reported on all types of life, including plants and animals, and even human studies, which have been comprehensively tabulated (Tables 1–3).[44–61] As the data show, most studies were conducted with cancer and diabetes cell lines and with people occupationally exposed to heavy metals.

In vitro studies related to miRNA alterations after Cd exposure

Altered patterns of miRNAs can cause changes associated with different health effects, offering that specific miRNAs are activated in pathophysiological processes. Recently, many *in vitro* studies have evaluated the correlation of environmental factors with miRNA expression. Table 1 summarizes the available studies in this area. Recently, Mortoglou *et al*. investigated the role of the miR-221, miR-155, and miR-126 in response to $CdCl_2$ in pancreatic ductal adenocarcinoma (PDAC) for 48 h with increasing concentrations of $CdCl_2$ (12 concentrations, 0–1 mM).[44] Among the oncogenic miRNAs in PDAC, miR-221 is mentioned together with miR-21,[62] while overexpression of miR-221 is related to several malignancies, including hepatocellular cancer,[63] prostate cancer, and colorectal carcinoma.[64,65] On the other hand, the upregulation of miR-221 is sharply associated with platelet-derived growth factor-mediated epithelial–mesenchymal transformation, migration, metastasis, and out-of-control proliferation phenotype of PDAC cells through mitogen-activated protein kinase inhibition and transforming growth factor beta signaling.[66] In addition, the increased expression of miR-155 also has been reported in PDAC tissue samples. In this regard, enhanced expression levels of miR-155 may result in poor survival of PDAC patients due to the induction of fibrogenesis by transforming growth factor beta.[67] Conversely, miR-126 is a tumor suppressor associated with PDAC progression via increased post-transcriptional expression of the genes Kirsten rat sarcoma virus and human epidermal growth factor receptor 2.[68,69] In a study by Mortoglou *et al*.,[44] the expression of miR-221 and miR-155 significantly increased after exposure to $CdCl_2$, while the expression of miR-126 decreased. An increase in epithelial–mesenchymal transformation was also observed due to the abnormal regulation of mesenchymal markers such as Wnt-11 and E-cadherin. Therefore, this study indicated that Cd may play an important role in the development of PDAC by showing a significant relationship between miRNAs and Cd exposure during disease progression.[44] Of course, more research is required to evaluate the exact role of miRNAs in the development of PDAC as well as the role of Cd and other environmental toxic contaminants. Cd is metabolized and reabsorbed poorly after filtration in the renal proximal tubules, which ultimately leads to its accumulation in the target tissues, with a half-life of 10–30 years. The intrarenal Cd concentration elevates over time until it reaches a cellular threshold associated with advanced renal cell damage.[70,71] Therefore, Cd has been particularly described as causing kidney damage in the general population and certain occupational populations exposed to Cd. Proteinuria, the first clinical symptom of Cd-induced renal damage, also occurs after low-level exposure to Cd.[71,72] In the later stages, tubular dysfunction progresses with nonspecific glomerular damage and eventually leads to a decrease in glomerular filtration. In addition, several investigations have shown a correlation between Cd exposure and chronic kidney disease.[72] Cd is also implicated in kidney carcinogenesis and has been categorized as a carcinogenic agent by the International Agency for Research on Cancer. The fundamental mechanisms of Cd poisoning related to kidney damage are partially known. Thus, in the cells, Cd elevates the generation of reactive oxidative species, which leads to oxidative stress, genome (DNA) damage, lipid peroxidation, and also apoptosis.[73,74] However, the identification of new regulatory mechanisms of Cd toxicity is most important to better assess the risks related to this common environmental pollutant and to develop new markers associated with Cd stress. Recent studies highlight the importance of miRNAs in kidney development or kidney pathogenesis. Therefore, a study was recently conducted to identify miRNAs that are differentially expressed in renal proximal tubule cells in response to Cd exposure. This study used two cell models to identify miRNAs whose expression was altered by Cd exposure, including: 1) renal proximal tubular epithelial cells (RPTECs)/human telomerase reverse transcriptase (hTERT) cells as a "discovery cell model" and 2) human kidney-2 cells as a "validation" cell model.[45] Of the 754 investigated miRNAs, 150 miRNAs were expressed in RPTECs/hTERT cells, of which the most expressed miRNAs were miR-222-3p, miR-21-5p, miR-146α-5p, miR-30c, and miR-30b-5p. As well as Cd significantly increased the expression of 38 miRNAs (Table 1). Notably, none of the investigated miRNAs was significantly decreased in cells exposed to Cd.[75] These findings suggest that Cd profoundly changes the expression of miRNAs in proximal tubular epithelial cells, and the abnormal expression of miRNAs may be involved in the molecular mechanisms of pathogenesis that occur during Cd-induced kidney injury. Further research in this field may allow the use of miRNAs as potential and promising markers of environmental stress. Another study used miRNA microarray and bioinformatics analysis to detect miRNAs that may mediate the regulation of phospholipase D1 (PLD1) expression and affect Cd-induced kidney injury.[76] The regulatory functions of the candidate miRNAs miR-122-5p and miR-326-3p were investigated in kidney injury using NRK-52E cells. Both of these miRNAs showed higher expression in all Sprague Dawley rats after 6 weeks of Cd exposure (subcutaneous injections of $CdCl_2$, 0.6 mg/kg, for 6 weeks). Cd treatment also elevated the expression of miR-122-5p and miR-326-3p as well as decreased the expression of PLD1 in NRK-52E cells. Both of these miRNAs can downregulate PLD1 expression by targeting it to the 3′-untranslated region and enhance Cd-induced apoptosis, while inhibition of either of them can reverse such effects. These results indicate that miR-122-5p and miR-326-3p can increase Cd-induced apoptosis of NRK-52E cells by downregulating PLD1 expression.[76] The results of the current study may introduce new targets for the prevention and treatment of Cd-induced kidney damage (Table 1).

Inflammation is a critical early event related to lung disease pathogenesis such as chronic obstructive pulmonary disease

Table 1. ***In vitro*** **studies investigating changes in miRNA expression with Cd exposure**

Sample for study	Dose and duration of Cd exposure	Altered miRNA expression	Results	Ref.
Control pancreatic cells (Panc-1 and MIA PaCa-2 cells) and a tumor	50 μM; 14 days	Upregulation: miR-221, miR-155; Downregulation: miR-126	1) miR-221 and miR-155 were upregulated in metastatic PDAC cell lines treated with cadmium chloride, while miR-126 was downregulated. 2) There is a significant association between miRNAs and Cd exposure during PDAC progression.	44
RPTECs, hTERT cells, and human kidney-2 cells	20 μM for human kidney-2 cells and 10 μM for RPTECs and hTERT cells; 24 h	Upregulation: miR-29c-3p, miR-376c-3p, miR-185-5p, miR-203a-3p, miR-132-3p, miR-27a-3p, miR-125b-5p, miR-301a-3p, miR-222-3p, miR-886-3p, miR-193a-5p, miR-99a-5p, miR-182-5p, miR-146b-5p, miR-21-5p, miR-324-5p, let-7a-5p, miR-146a-5p, let-7b-5p, miR-181a-5p, miR-362-5p, miR-15a-5p, miR-28-3p, miR-328-3p, miR-455-5p, miR-20a-5p, miR-34a-5p, miR-652-3p, miR-30c-5p, miR-26b-5p, miR-183-5p, miR-708-5p, miR-130a-3p, miR-886-5p, miR-99b-5p, miR-31-5p, miR-660-5p, miR-30b-5p	1) Increased expression of 38 miRNAs in RPTECs and hTERT cells was observed. 2) The target genes of many of these miRNAs encode proteins that are involved in oxidative stress, inflammation, and apoptosis.	45
Ovarian granulosa cells of ICR mice	10, 20, and 40 μM; 2, 4, 6, and 8 h	Upregulation: miR-384-3p, miR-153-3p, miR-338-3p, miR-551b-3p, miR-129-1-3p, miR-129-5p, miR-9-5p, miR-496a-3p, miR-135a-5p, miR-539-5p, miR-344-3p, miR-379-3p, miR-126a-3p, miR-219a-2-3p, miR-128-3p, miR-218-5p, miR-326-3p, miR-380-3p, miR-376a-3p, miR-376a-5p, miR-543-3p, miR-741-3p, miR-488-3p, miR-190a-5p, miR-3473b, miR-3473a, miR-138-5p, miR-29c-5p, miR-330-5p, miR-410-3p, miR-376b-3p, miR-7b-5p. Downregulation: miR-202-5p, miR-322-3p, miR-1953, miR-450a-2-3p, miR-5121, miR-712-5p, miR-302d-3p, miR-5625-3p, miR-375-3p, miR-672-5p, miR-25-3p, miR-291a-3p, miR-M1–5-5p, miR-19a-3p, miR-489-5p, miR-1912-5p, miR-196a-5p, miR-5099, miR-1894-3p, miR-346-5p, miR-19b-3p, miR-20b-5p, miR-27a-3p, miR-542-5p, miR-93-5p, miR-202-3p	1) The target gene functions of 29 miRNAs mainly include the regulation of cell metabolism, post-transcriptional messenger RNA regulation, IL6-mediated signal transduction, cell cycle, proliferation, differentiation, and migration. 2) These miRNAs are associated with target genes related to Ras, Rap1, Foxo, Hippo, mitogen-activated protein kinase, and the carcinogenic pathway, regulation of actin cytoskeleton, stem cell signaling pathway polymorphism, and local adhesion leading to cell division and tumorigenesis.	46
Human primary proximal tubule epithelial cells	25 μM; 6 and 24 h	Upregulation: miR-132-3p; Downregulation: miR-146b-5p, miR-18a-5p	1) Increased expression of miR-132-3p after 6 h. 2) Increased expression of miR-132-3p after 24 h.	47
Human prostate epithelial cells transformed with Cd	10 μM; 8 weeks	Upregulation: miR-96, miR-134, miR-9; Downregulation: miR-125a-5p, miR-222, let-7b, miR-205, miR-20a, miR-146b-5p, miR-138, miR-373	1) 12 and 3 miRNAs had decreased and increased expression, respectively. 2) These data show that the expression of miRNAs with altered expression may be important in the transformation process of the malignant prostate epithelium by Cd.	48
Hepatoma cell line (HepG2)	0.1–10 μM cadmium chloride; 24, 48, and 72 h	Upregulation: hsa-mir-138 and hsa-mir-372	Analysis of miRNAs showed that the increased expression of miR-372 can affect the expression of p21 and promote cell cycle progression and proliferation.	49

(continued)

Table 1. *(continued)*

Sample for study	Dose and duration of Cd exposure	Altered miRNA expression	Results	Ref.
Cell line BALB/3T3 A31-1-1	2.4 µM cadmium chloride with lead and arsenic; 4 h	Upregulation: miR-154, miR-10, miR-222, miR-375, miR-133, miR-204, miR-379	The results show that this metal mixture led to altered expression of miRNAs, which may be responsible for changes in messenger RNA expression that encode proteins involved in cellular processes, including cell death, growth, proliferation and inflammation associated with heavy metals.	50
Human lung epithelial cell line and normal bronchial epithelial cells	Cd; 24 h	Downregulation: miR-181a-2-3p	1) The results showed that the expression of miR-181a-2-3p was significantly decreased in cells treated with Cd, and the silencing of miR-181a-2-3p increased the inflammatory responses and Cd-induced inflammation. 2) It was found that the negative regulatory effect of miR-181a-2-3p on inflammation is partially mediated by the calcium signaling pathway. 3) miR-181a-2-3p knockdown followed by Cd exposure significantly increased the expression levels of inflammatory cytokines such as IL1α, IL1β, IL6, IL8, tumor necrosis factor alpha, and increased cyclooxygenase 2.	51
NRK-52E cells (a rat kidney epithelial cell line)	10 µM; 48 h	Upregulation: miR-375-3p, miR-196c-3p, miR-155-5p, miR-34a-5p, miR-210-3p, miR-17-1-3p, miR-183-5p, miR-203b-3p, miR-199a-5p, miR-146b-5p, miR-132-3p, miR-20b-5p, miR-21-5p, miR-92b-3p, miR-182, miR-26b-5p, miR-379-5p, miR-326-3p, miR-193-5p, miR-3562, miR-18a-5p, miR-31a-5p, let-7d-3p, miR-1224, miR-222-3p, miR-19b-3p, miR-346, miR-221-3p, miR-489-3p, miR-30c-1-3p, miR-223-3p, miR-6324, miR-532-5p, miR-196c-5p, miR-200c-3p, miR-92a-3p, miR-219a-2-3p, miR-29b-3p, miR-212-3p, miR-547-5p,miR-214-3p, miR-449c-5p, miR-532-3p; Downregulation: miR-344g, miR-122-5p, miR-664-1-5p, miR-382-5p, miR-702-5p, miR-342-5p, miR-503-5p, miR-350, miR-27b-5p, miR-192-3p, miR-874-3p, miR-708-5p	1) Cd treatment also increased miR-122-5p and miR-326-3p and decreased PLD1 in NRK-52E cells. 2) The results suggest that miR-122-5p and miR-326-3p may enhance Cd-induced NRK-52E cell apoptosis through downregulating PLD1 expression.	52
LLC-PK1 cells	20 µM; 12 h	Upregulation: n = 160 miRNAs; Downregulation: n = 25 miRNAs	1) miR-125a/b plays a key role in the suppression of Cd-induced apoptosis by selenium through the mitochondrial pathway.	53

Cd, cadmium; hTERT, human telomerase reverse transcriptase; IL, interleukin; miR or miRNA, microRNA; PDAC, pancreatic ductal adenocarcinoma; PLD1, phospholipase D1; RPTECs, renal proximal tubular epithelial cells.

Table 2. ***In vivo*** **studies investigating miRNA expression changes with Cd exposure**

Sample for study	Dose and duration of Cd exposure	Altered miRNA expression	Results	Ref.
Male Sprague Dawley rats	0.6 mg/kg of cadmium chloride; 12 weeks	Upregulation: miR-3084a-3p, miR-34a-5p, miR-1949, miR-224-5p, miR-222-3p, miR-221-3p, miR-146b-5p, miR-210-5p, miR-20a-5p, miR-146a-5p, miR-3084c-3p, miR-92a-3p, miR-21-5p, miR-466b-2-3p, miR-320-3p, miR-15b-5p, miR-466c-3p, miR-214-3p, miR-483-5p, miR-149-3p, let-7i-5p, miR-762, miR-466d, miR-346, miR-17-5p, miR-451-5p, miR-92b-3p, miR-466c-5p, miR-32-3p; Downregulation: miR-193b-3p, miR-185-5p, miR-455-3p, miR-195-5p, miR-200a-3p, miR-101 b-3p, miR-194-5p, miR-99a-5p, miR-505-3p, miR-342-3p, miR-203a-3p, miR-378a-3p, miR-378a-5p, miR-140-5p, miR-378b, miR-103-3p, miR-107-3p, miR-192-5p, miR-152-3p, miR-100-5p, miR-30a 3p, miR-30a-5p, miR-22-5p, miR-30b-5p, miR-196b-5p, miR-489-3p, miR-30e-5p	1) Cd-altered miRNAs may be used as urinary biomarkers for Cd-induced kidney damage.	54
Sprague Dawley rats	0.6 mg/kg; 12 weeks	Upregulation: miR-3084a-3p, miR-224-5P, miR-222-3P, miR-221-3P, miR-146b-5p, miR-210-5p, miR-20a-5p, miR-146a-5p, miR-3084c-3p, miR-92a-3p, miR-21-5P, miR-466-2-3P, miR-320-3p, miR-15b-5p, miR-466c-3p, miR-214-3p, miR-483-5p, miR-149-3p, let-7i-5p, miR-762, miR-466d, miR-346, miR-17-5p, miR-451-5p, miR-92b-3p, miR-466c-5p, miR-32-3p miR-34a-5p, miR-1949; Downregulation: miR-193b-3p, miR-185-5p, miR-455-3p, miR-195-5p, miR-200a-3p, miR-101b-3p, miR-194-5p, miR-99a-5p, miR-505-3p, miR-342-3p, miR-203a-3p, miR-378a-3p, miR-378a-5p, miR-140-5p, miR-378b, miR-103-3p, miR-107-3p, miR-192-5p, miR-152-3p, miR-100-5p, miR-30a-3p, miR-30a-5p, miR-22-5p, miR-30b-5p, miR-196b-5p, miR-489-3p, miR-30e-5p	1) Cd significantly changes the miRNA expression profile in the renal cortex. 2) Cd-induced dysregulation in the miRNA profile might be used as a urinary biomarker of Cd exposure or Cd-induced kidney injury	55
Daphnia pulex	20 (low concentration) and (high concentration) 40 µL/L of cadmium chloride; 48 h	*Cd in high doses* – Upregulation: miR-194, miR-278, miR-2441, miR-71, miR-204, miR-210, miR-252, miR-279, miR-615, miR-1076, miR-1414, miR-2219, miR-6831; Downregulation: miR-144, miR-216, miR-7670, miR-194, miR-7939, miR-344, miR-345, miR-6743, miR-7444. *Cd in low doses* – Upregulation: miR-92, miR-871, miR-1894, miR-7666, miR-4259, miR-7422, miR-71, miR-204, miR-210, miR-252, miR-279, miR-615, miR-1076, miR-1414, miR-2219, miR-6831; Downregulation: miR-217, miR-7653, miR-344, miR-345, miR-6743, miR-7444	1) 21 and 22 miRNAs under a low concentration (20 µg/L) and a high concentration (40 µg/L) of cadmium chloride, respectively, had different expression levels compared to the control group. 2) Cellular functions of predicted target genes of Cd-responsive miRNAs include oxidative stress, ion transport, mitochondrial damage, and DNA repair.	56
Chicken spleen	10 mg/kg of cadmium chloride in food; 90 days	Downregulation: miR-33-5q	1) Cd induced deregulation of the miR-33/ adenosine monophosphate-activated protein kinase axis, leading to Bcl-2-interacting protein 3-dependent autophagy in the chicken spleen through the protein kinase B/mammalian target of rapamycin and heat shock protein 70-nuclear factor kappa B/ c-Jun N-terminal kinase signaling pathways. 2) In addition, Cd can affect ion homeostasis in the chicken spleen.	57
Freshwater crab *Sinopotamon henanense*	0.5 mg/L, 30 days	Upregulation: miR-44-3p, miR-45-3p, miR-3878, miR-2419, miR-5124, miR-1684-3p, miR-34-3p, miR-5106-3p, miR-6364-3p, miR-1-3p, miR-281, miR-4968, miR-46-3p, miR-281-3p, miR-7, miR-993-3p, miR-4206-3p, miR-6491, miR-6963, miR-2765, miR-8485-3p, miR-965-3p, miR-12, novel-m0106, novel-m0089-3p, novel-m0012-3p, novel-m0104, novel-m0121-3p, novel-m0169-3p, novel-m0158-3p, novel-m0053-3p; Downregulation: miR-6907-3p, miR-145, miR-124-3p, miR-3897-3p, miR-216, miR-14-3p, miR-1307, miR-619-3p, miR-335, miR-981-3p, miR-155, miR-203-3p, miR-2779, miR-874-3p, miR-140, novel-m0084, novel-m0142, novel-m0113, novel-m0148, novel-m0150-3p	1) 51 miRNAs with differential expression were identified in the Cd-exposed group. 2) 31 miRNAs had increased expression and 20 miRNAs had decreased expression. 3) Altered expression of miRNAs may be an adaptation to resist Cd-induced oxidative stress.	58

Cd, cadmium; miR or miRNA, microRNA.

Table 3. Human studies investigating miRNA expression changes with Cd exposure

Sample for study	Dose and duration of Cd exposure	Changed miRNA expression	Results	Ref.
Blood	Serum Cd levels in bladder cancer patients compared to controls	Upregulation: miRNA-21	1) Among the cancer group, miRNA-21 had increased expression in cancerous tissues compared to adjacent noncancerous tissues. 2) There is a relationship between body Cd burden and tissue expression of miRNA-21 in patients, indicating the role of miRNA-21 in Cd-induced bladder cancer.	59
Blood	Occupationally exposed to Cd	Upregulation: miR-221	1) miR-221 was significantly higher in the exposure group, with a 3.05-fold change. 2) miR-221 and miR-155 showed a positive and significant correlation with T-helper cells. 3) Increased expression of miR-221 was associated with immune changes, making it a potential candidate for further studies of the underlying mechanism of Cd toxicity.	60
Blood and urine	Occupational chronic Cd poisoning subjects	Upregulation: miR-363-3p; Downregulation: miR-122-5p, miR-129-5p, miR-204-3p, miR-361-3p	1) 5 miRNAs were detected with expression changes. 2) Increased miR-363-3p is associated with downregulation of phosphoinositide 3-kinase, suppression of proliferation, and increased apoptosis of renal tubule epithelial cells.	61

Cd, cadmium; miRNA or miR, microRNA.

(COPD). Increasing data suggest that miRNAs play a role in the pathogenesis of COPD through regulation of the inflammatory response. In 2019, a study was conducted to investigate the role of miR-181a-2-3p in Cd-induced inflammation in human bronchial epithelial cells.[77] This study aimed to identify new miRNAs that affect the molecular targets of COPD and to investigate the molecular mechanisms of the airway inflammatory state. The results showed decreased expression of miR-181a-2-3p in lung tissues and in the serum of COPD patients compared with control normal subjects. In addition, the upregulation of miR-181a-2-3p in airway cells increased the inflammatory response in Cd-treated cells.[77] These findings suggest an important role of miR-181a-2-3p in humans and their potential target genes (TRL4 and SQSTM1), emphasizing the pathophysiological consequences of airway inflammation in COPD. Other *in vitro* studies with various cell lines, including murine ovarian granulosa cells,[46] human primary proximal tubule epithelial cells,[47] Cd-transformed human prostate epithelial cells, and hepatoma cells, have been carried out with specific objectives during the last decade, and the findings of each study along with the altered miRNAs are summarized in Table 1.[48,49]

In vivo studies related to miRNA alterations after Cd exposure

Exposure to inorganic Cd is a global problem. A few *in vivo* investigations have assessed the potential effect of miRNAs in organisms in response to Cd stress, and several differentially expressed genes have been discovered. Several studies also have investigated changes in the expression profile of miRNAs in plants exposed to Cd, but this article only reviewed animal studies. *In vivo* studies of miRNA expression changes after Cd exposure are summarized in Table 2. The nephrotoxic metal Cd is a carcinogenic heavy metal currently ranked seventh on the 2017 Agency for Toxic Substances and Disease Registry Hazardous Substances List and the 2017 U.S. Environmental Protection Agency Hazardous Substances List. Circulating Cd bound to proteins or thiol compounds is filtered in the glomeruli and absorbed into the epithelial cells of the proximal tubule, and chronic human exposure to Cd causes accumulation in the proximal tubule.[78] When exposure to Cd reaches a critical level, toxic damage characterized by widespread resorption can occur, eventually leading to polyuria and proteinuria. Although the toxic influences of Cd on the proximal tubule have been studied, the molecular and cellular mechanisms involved in Cd-induced kidney damage have not been well elucidated. Before inducing cell death, Cd has been reported to induce oxidative stress, confuse cadherin-dependent cell-to-cell adhesion, activate several cell signaling pathways, and promote endoplasmic reticulum stress and autophagy in the proximal tubule.[72,79] Although Cd can affect many cellular processes, it is not well understood how miRNAs may contribute in Cd-induced proximal tubular epithelial cell damage. Fay *et al*. conducted a study on Cd-stressed male Sprague Dawley rats and reported that Cd nephrotoxicity is correlated with altered miRNA expression in the rat renal cortex.[54] The results of the microarray analysis showed that the expression of 44 miRNAs was remarkably enhanced and the expression of 54 miRNAs was remarkably reduced in the Cd-treated group compared to the control.[54] These results show that Cd significantly changes the expression profile of miRNAs in the renal cortex and raises the probability that dysregulated expression of these miRNAs may play a role in the pathophysiology of renal injury caused by Cd toxicity. In addition, these obtained results raise the possibility that Cd-modified miRNAs can be applied as potential bio-urinary markers of Cd exposure or Cd-induced kidney damage. Cd metal is also very toxic to aquatic organisms, and research has been done in this field. *Daphnia pulex* is a continental crustacean that is broadly used as a model in toxicological studies.[80] Recent investigations indicate that miRNAs play an incredible role in the response of animals to toxic heavy metals. To this end, in recent years, researchers have used microarrays to analyze the miRNA expression profiles of *D. pulex* after 48 h of exposure to Cd. This study identified 22 and 21 miRNAs with differential expression after exposure to low-dose (20 μg) and high-dose (40 μg) Cd, respectively. There were 16 and 6 miRNAs whose expression was increased in the groups with low and high doses of Cd, respectively. On the other hand, 13 and 8 miRNAs with decreased expression were detected under low and high Cd concentrations, respectively.[81] Ten of these altered miRNAs were miR-71, miR-204, miR-210, miR-252, miR-279, miR-614, miR-1414, miR-1076, miR-2219, and miR-6831.[81] These findings indicate that these miRNAs, especially miR-71 and miR-210, have conserved roles in Cd-induced cellular responses. For instance, miR-71 has been identified as an inhibitor of calcium ion (Ca^{2+}) signaling, and upregulation of miR-71 can inhibit

Ca^{2+} signaling.[82] These results are important findings because Cd acts as a Ca^{2+} antagonist that can block Ca^{2+} channels.[83] In addition, miR-71 contributes to the regulation of stress response and lifespan.[84] Therefore, the increased expression of miR-71-dpu in *Daphnia* exposed to Cd suggests that this miRNA plays an important role in Cd-induced Ca^{2+} disturbances. Also, in this regard, the predicted target genes show that miR-210 and miR-71 are likely involved in Cd-induced changing ion homeostasis via targeting several important ion transport proteins such as ATP2C2 and Ca-P60A.[81] Among the miRNAs with reduced expression in the present study, miR-144 is known as a lithium-responsive gene that can modulate oxidative stress responses.[85,86] Therefore, the decreased expression of this miRNA in the high-dose Cd-exposed group may be associated with the oxidative stress response induced by Cd.[87] The predicted target genes are involved in oxidative stress, ion transport, mitochondrial damage, and DNA repair. Additionally, ingenuity pathway analysis was performed in this study, which identified a significant network (p-score = 22, $p = 10^{-22}$) containing several Cd-responsive miRNAs related to insulin metabolism.[81] Overall, this study adds to our information on the role of miRNAs in response to toxic metal exposure. Another study analyzed the transcriptional profile of miRNAs in freshwater crayfish to assess their expression levels in response to Cd (0.5 mg/L Cd for 30 days) toxicity.[88] Overall, this study identified 51 miRNAs with altered expression, of which 31 and 20 miRNAs were identified with increased and decreased expression, respectively. Moreover, gene ontology analysis of target genes demonstrated the importance of regulating the activity of oxidoreductases. Also, Kyoto Encyclopedia of Genes and Genomes pathway analysis showed that 18 pathways were remarkably enriched, which were mainly related to protein biosynthesis, protein modification, and protein degradation. Finally, it can be concluded that the expression of many miRNAs was altered in response to Cd toxicity in the studied model, which may be an adaptation program to resist Cd-induced oxidative stress.[89] These findings provide a basic design for further investigations on the functional adaptation of animals to mediate miRNAs to combat Cd toxicity. *In vivo* studies to investigate changes in the expression of miRNAs with Cd exposure are summarized in Table 2.

Human studies related to miRNA expression after Cd exposure

It has been shown that miRNAs can control gene expression and regulate important pathways in cells.[90] According to research, miRNAs also have amazing roles in the formation and development of cancer. Evidence shows that exposure to toxic metals affects their expression.[91] It has been reported that miR-21 is one of the most common miRNAs with increased expression in different types of cancers in humans; it operates as a main regulator in the process of carcinogenesis and is considered to be a new target for cancer monitoring.[50] Interestingly, recent studies also show that miR-21 plays an important role in heavy metal-induced cellular malignancy and tumorigenesis. Studies have demonstrated a link between miRNA expression changes and Cd carcinogenesis in various cancers, including pancreatic cancer and ovarian cancer.[92,93] These metals also increase the risk of urinary carcinogenesis.[94] The exact carcinogenic mechanism of Cd and Pb has not yet been fully elucidated.[59] Changes in oxidative stress and the inability to repair DNA can lead to genetic mutations that are associated with abnormal gene expression and affect cancer prognosis.[95] Moreover, some studies have shown the cancerous transformation of human urothelial cell lines upon exposure to Cd. In this regard, a recent study investigated the relationship between blood Cd and Pb concentrations and miR-21 expression in patients with bladder cancer.[96] In this study, the concentrations of Cd and Pb in the blood were determined in 268 bladder cancer patients and 132 controls using inductively coupled plasma optical emission spectroscopy. The blood Cd and Pb concentrations were interpreted based on the type and stage of cancer. Next, this research group assessed miR-21 expression in adjacent noncancerous and cancerous tissues by reverse transcription–quantitative polymerase chain reaction in cohorts. The results indicated that the concentrations of Pb and Cd in patients with cancer had increased levels compared to the controls. This increase was also found to be greater in the muscle-invasive bladder cancer subjects than in the nonmuscle-invasive bladder cancer group. miR-21 expression in cancer tissues was significantly associated with the blood Cd and Pb concentrations in patients. The positive and significant correlation between blood Cd and miR-21 expression in the transitional cell carcinoma and squamous cell carcinoma groups indicates that these metals play a role in the genetic changes associated with bladder cancer. These data are consistent with other literature reports showing the participation of miR-21 in metal-induced carcinogenesis.[96] According to the results published in the discussed study, there is an association between Cd and Pb burden and miR-21 tissue expression in bladder cancer patients, thus indicating a role for miR-21 in Cd- and Pb-induced bladder cancer. Recently, Goyal *et al*. investigated the relationship of miRNA expression with immune marker changes in workers exposed to Cd.[60] Recently, many *in vivo* and *in vitro* experiments have shown expression changes in the miRNAs of workers exposed to Cd.[97] Differential expression of miRNAs also has been discovered in carcinogenesis induced by Cd. Because changes in circulating miRNAs can be applied as a potential biomarker (including diagnostic and prognostic markers) and miR-20b, miR-155, and miR-221 contribute to the process of apoptosis and immune homeostasis, these miRNAs can be related to inflammation-induced cancer. In this study, the differences in the expression of these three miRNAs in immune cells (T helper (Th) 1, Th17, and regulatory T cells) were investigated, and the levels of cytokines including interleukin (IL) 2, IL4, IL6, IL10, IL17, and tumor necrosis factor alpha were studied. The premise of the study was that Cd exposure may trigger changes in the expression of miRNAs in serum, which can reflect changes in the expression profile of immunity markers. In the referred study, 106 workers in craft and metal welding factories and 80 healthy people who were not exposed to Cd were selected as subjects. The blood Cd levels were determined through an atomic absorption spectroscopy platform.[97] Some lymphocyte cells were determined by flow cytometry, the serum IL expression levels were analyzed by enzyme-linked immunosorbent assays, and miRNA expression levels were assessed by a polymerase chain reaction method. The results indicated that the blood levels of Cd were significantly higher in Cd-exposed people compared to unexposed people, with the highest level among welders. Among lymphocyte subsets, the exposed group had significantly higher levels of Th17, while the regulatory T cell population had a lower percentage. The anti-inflammatory responses became the main way of profiling cytokines expressed by workers exposed to Cd. Among the studied miRNAs, miR-221 was significantly elevated in the exposed group, with a fold change of 3.05. In addition, miR-221 and miR-155 had a positive and significant relationship with Th17 immune cells. Further analysis also showed that the duration of Cd exposure and IL17 significantly affected the expression of miR-221 in the exposed group.[97] In summary, miR-221 was remarkably increased under Cd exposure conditions and was associated with changes in the immune system,

presenting it as a possible candidate for the mechanism underlying Cd toxicity for further studies. The results of studies in this field show that toxicity with heavy metals, including Cd, can change the expression profile of miRNAs, and finally their abnormal expression can lead to disruptions in the immune system and cellular homeostasis. Therefore, more research is needed in this area for different diseases. In addition, the evaluation of downstream target genes of changed miRNAs in a larger population can open new and comprehensive insights to understand the toxicity of Cd and consequent human susceptibility to disorders such as cancer and immune-related diseases. Furthermore, appropriate measures and necessary treatment should be considered to protect people exposed to Cd to avoid adverse health effects. Cd chronically enters into the body and gathers in organs over the years. In this regard, the renal system organs are the first to be affected by Cd toxicity, so nephrotoxicity features of Cd primarily damage the proximal tubules and causes proteinuria. Cd can also increase renal secretion of proteins including β-2-microglobulin and retinol-binding protein.[73] Considerable efforts have been made to repair kidney damage caused by Cd toxicity. However, metal antidotes are ineffective against this defect because renal failure is progressive and irreversible when urinary Cd levels exceed 10 mg/g creatinine.[59] Therefore, studying renal signaling molecules induced by Cd is an important step towards the development of new therapeutic strategies. In this regard, a study was conducted in 2021 to analyze the effects and detailed mechanisms of miRNAs involved in nephrotoxicity induced by Cd in occupational workers.[60] The results showed that the expression of miR-363-3p was increased in the serum of these patients. This miRNA is an important tumor suppressor in various carcinomas such as liver carcinoma, thyroid carcinoma, lung carcinoma, and colorectal cancer. This study also observed that an increase in miR-363-3p is associated with a decrease in phosphoinositide 3-kinase expression and an increase in renal tubular epithelial cell proliferation and apoptosis.[60] The results obtained indicate the involvement of this miRNA in the pathophysiology of Cd-induced kidney damage in humans and can be considered in future interventional therapeutic options for the treatment of Cd-related kidney injury. Human studies of altered miRNA expression by Cd are summarized in Table 3.

Conclusions

Dysregulation of miRNAs has recently been reported to play an important role in the pathogenesis of diseases caused by heavy metal exposure. The functionality effects of miRNAs are mediated by their target proteins, so investigating the expression of potential target proteins is important to comprehensively understand the role and mechanism of miRNAs in heavy metal-induced diseases. In summary, this review article discusses the influence of Cd on miRNA alterations in humans, *in vivo* models, and cell lines. These changes may affect targets in several biological pathways, contributing to disease progression. Regrettably, there is not a consensus on a consistent profile of miRNA expression for Cd-induced pathological conditions, especially because the majority of the investigations analyze targeted miRNAs rather than the whole genome. A distinct miRNA profile might be hopeful as a biomarker for exposure, diagnosis, prognosis, and treatment efficacy. Furthermore, this review demonstrates that miRNA expression alterations are common among diverse experimental models such as humans, animals, and cell lines, which may be useful for designing new studies to better understand metal-induced pathogenic mechanisms and related pathways. In addition, we emphasize the need for experimental disease models describing more complex human diseases, such as neurodegenerative diseases and cancer, to identify new miRNA-based biomarkers influenced by Cd. In conclusion, the identification and analysis of miRNAs responding to different toxic metals provide valuable information about their possible relationships in the networks associated with living organisms exposed to these abiotic stresses.

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Conflict of interest

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Author contributions

Contribution to the conception and design of the work and literature review (NAD, MK), All authors wrote the first draft, revision and editing (MF, MRT). All authors approved the final version of the manuscript.

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