Journal of Biosciences and Medicines, 2026, 14(3), 204-234
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Emerging Roles of DNA Methylation and Non-Coding RNAs in Arsenic Toxicity

Jiamin Yuan[1*], Jiao Dai[2*], Rongxian Li[1], Zuoshun He[1], Shiyan Gu[1#]

[1]Institute of Preventive Medicine, School of Public Health, Dali University, Dali, China
[2]Qujing Medical College, Qujing, China
Email: [#]ygsy727@163.com

How to cite this paper: Yuan, J.M., Dai, J., Li, R.X., He, Z.S. and Gu, S.Y. (2026) Emerging Roles of DNA Methylation and Non-Coding RNAs in Arsenic Toxicity. *Journal of Biosciences and Medicines*, **14**, 204-234.
https://doi.org/10.4236/jbm.2026.143016

Received: January 12, 2026
Accepted: March 6, 2026
Published: March 9, 2026

Abstract

Arsenic and related derivatives are pervasive metalloid contaminants in the environment, capable of infiltrating the biosphere via air, water, and soil. Crops and their derivatives are susceptible to contamination, which is conveyed to the human body via the food chain. Furthermore, arsenic can be directly inhaled or ingested through the respiratory and digestive tracts. Consequently, food safety concerns related to arsenic and its constituents, along with the associated health risks, have garnered heightened scrutiny. Exposure to arsenic can result in both acute and chronic toxicity, inflicting harm on various organs and systems. Numerous studies have demonstrated that arsenic and its compounds contribute to arsenic poisoning via DNA methylation and the modulation of non-coding RNAs (ncRNAs), resulting in the onset and progression of numerous disorders. This review will elucidate the mechanisms of DNA methylation, long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs) in relation to arsenic toxicity.

Keywords

Arsenic Toxicity, DNA Methylation, lncRNAs, miRNAs, circRNAs

1. Introduction

Arsenic (As) is a hazardous metalloid that occurs in the environment in both organic and inorganic forms [1]. Inorganic forms are frequently observed to be more reactive and hazardous than their organic counterparts. Inorganic arsenic is the primary pollutant, predominantly in the +3 or +5 oxidation states. In these phases, inorganic arsenic forms sulfur complexes or oxygen anions, specifically arsenite

*Co-first authors.
#Corresponding author.

(As^{III}) and arsenate (As^{V}) [2]. Organic compounds such as arsenic betaine, arsenosugars, and arsenolipids predominantly occur in fish [3]. Arsenic's distinctive chemical features facilitate its migration in the environment, allowing it to infiltrate surface water and groundwater systems, thereby contaminating drinking water supplies [4]. The utilization of arsenic-contaminated groundwater for agricultural irrigation may result in the accumulation of arsenic in both soil and crops, ultimately causing significant worldwide health issues [5]. Approximately 150 million individuals globally are projected to be at risk of arsenic pollution in their drinking water. In Bangladesh, China, India, Chile, and Argentina, the arsenic levels in groundwater are significantly elevated, constituting a huge health concern for tens of millions of individuals [6]. Arsenic is a multi-organ toxic contaminant, and prolonged exposure to inorganic arsenic via drinking water, contaminated food, and air can adversely impact various organs or systems, including the liver, kidneys, lungs, bladder, skin, nervous system, cardiovascular system, and reproductive system, significantly influencing chronic diseases in humans [7] [8]. The processes underlying arsenic toxicity remain incompletely elucidated; nevertheless, an increasing body of research indicates that arsenic can affect gene expression related to its toxicity via epigenetic pathways [9] [10].

Epigenetic modifications are inheritable alterations that influence gene expression without changing the DNA sequence and are crucial for appropriate development and gene control [11]. Several significant epigenetic mechanisms have been recognized: DNA methylation, RNA methylation, histone modification, and noncoding RNA (ncRNA) control. NcRNAs primarily consist of long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs) [12]. Recently, DNA methylation, miRNAs, lncRNAs, and circRNAs have emerged as focal points in the investigation of arsenic toxicity mechanisms. Their particular regulation systems remain unclear. This work is to synthesize recent research findings and clarify the mechanisms of DNA methylation, miRNAs, lncRNAs, and circRNAs in arsenic toxicity. It enhances the comprehensive understanding of arsenic's harmful effects on many tissues and organs, serving as a significant reference for environmental toxicology and health risk evaluation. It may uncover novel therapeutic targets and offer innovative treatment techniques for arsenic toxicity and arsenic-induced ailments.

2. Roles of DNA Methylation in Arsenic Toxicity

DNA methylation, a principal type of epigenetic modification, constitutes a chemical alteration of DNA in eukaryotes [13]. The process is facilitated by DNA methyltransferase (DNMT), which attaches a methyl group to the 5th carbon of the cytosine ring, resulting in the formation of 5-methylcytosine (m^5C), utilizing S-adenosylmethionine (SAM) as the methyl donor [14]. This alteration is typically concentrated in particular DNA sequence areas, such as CpG islands [15]. DNA methylation can modify chromatin architecture, DNA conformation, and stability, influencing DNA-protein interactions and significantly contributing to gene

regulation and animal development [16]. In humans, DNA methylation is primarily catalyzed by DNMT3A and DNMT3B, which facilitate the de novo methylation process, whereas DNMT1 is responsible for preserving the established methylation state [17]. DNA methylation is categorized into genome-wide DNA methylation and promoter region DNA methylation. Studies indicate that DNA methylation patterns represent the most prevalent epigenetic modifications linked to arsenic exposure [6]. Arsenic can directly or indirectly modulate the expression and activity of DNMTs, leading to modified methylation levels throughout the genome or in the promoter regions of particular genes [18]. Furthermore, arsenic may disrupt normal DNA methylation by competing for methyl groups provided by SAM [1].

2.1. Roles of DNA Methylation in Arsenic-Induced Hepatorenal Toxicity

The liver is among the organs most impacted by arsenic exposure and metabolism, with chronic arsenic consumption potentially resulting in liver damage [19]. Numerous investigations have verified that arsenic exposure can result in substantial changes in hepatic DNA methylation. In the livers of C57BL/6J (B6) and 129X1/SvJ (129) mouse strains subjected to acute $NaAsO_2$ intoxication, inter-strain variations in the expression levels of DNMTs and genome-wide DNA methylation levels were observed. However, both demonstrated genome-wide DNA hypomethylation following weeks of arsenic exposure [20]. Arsenic exposure may induce hypermethylation of critical gene promoter regions in the liver. For instance, DNA repair genes like ERCC2 and RPA1, along with gene promoter areas of the Wnt signaling pathway such as c-MYC and WNT2B, exhibited notable hypermethylation in arsenic-exposed human liver (L-02) cells [21]. Subsequent examination of $NaAsO_2$-induced liver fibrosis models indicated that 12,083 genes exhibited hypermethylation, encompassing promoter-specific hypermethylation of ferroptosis-related genes such as SLC7A11 and CDKN1A, potentially linked to arsenic-induced pathological alterations in the liver [22]. Alongside the promoter hypermethylation phenomena, substantial decreases in total DNA methylation levels were noted in the livers of fish, mice, and rats subjected to continuous exposure to inorganic arsenic [23]. Arsenic has been demonstrated to influence cell cycle regulating genes, including P21, by modifying DNA methylation. Subsequent research indicated that human hepatocellular carcinoma cells (HepG2) exhibited a decrease in overall DNA methylation levels following prolonged low-dose exposure to $NaAsO_2$ (10 - 20 days). Simultaneously, the expression of DNMT1 and DNMT3B was upregulated, but DNMT3A expression was marginally downregulated [23]. The epigenetic effects of arsenic exhibit notable gender and generational disparities. Cross-generational genetic studies indicate that the ingestion of arsenic-laden water during pregnancy and lactation in F0-generation female rats resulted in pronounced DNA methylation dysregulation in the liver of F1-generation male rats. Conversely, F2-generation females exhibited increased sensitivity

[24].

The kidneys are the primary organs for arsenic absorption, accumulation, and excretion, making them vulnerable to arsenic-induced damage; arsenic exposure may precipitate various forms of renal failure [25]. A case-control study of individuals with chronic kidney disease (CKD) revealed a positive correlation between LINE-1 methylation levels and the severity of CKD. The concentration of urine arsenic was strongly linked with the methylation level of LINE-1. This indicates that arsenic exposure may contribute to the onset of chronic kidney disease via alterations in DNA methylation status [26]. A separate study revealed that Human Kidney Proximal Tubular Epithelial (HK-2) Cells exhibited pathological characteristics of fibrosis following exposure to $NaAsO_2$, alongside a notable upregulation of DNMT3a and DNMT3b expression [27].

2.2. Roles of DNA Methylation in Arsenic-Induced Reproductive Toxicity

Research indicates that arsenic exposure from gestation to the neonatal phase disrupts normal organ development and may result in miscarriage, stillbirth, and congenital anomalies of the reproductive organs [28]. A genome-wide investigation of neonatal cord blood in the New Hampshire Birth Cohort revealed that even minimal prenatal arsenic exposure influenced CpG island methylation in neonatal cord blood. Subsequent study demonstrated a linear correlation between the methylation levels of various CpG islands and maternal urine arsenic concentrations. The effect was more pronounced in males than in females, indicating gender disparities [29]. Maternal urinary arsenic levels correlated with the methylation of promoter regions of genes including P16, P53, and LINE-1 in cord blood [30]. A Mexican study indicated that prenatal arsenic exposure correlated with diminished DNA methylation levels at specific CpG loci (CpG15, CpG19, and CpG21) of the C18ORF8 gene [31]. In utero, arsenic exposure can result in global DNA hypomethylation, hypomethylation of Cyclin D1, and hypermethylation of Tp53 [32]. Furthermore, prenatal arsenic exposure shown a negative correlation with gestational age and birth weight, an effect mediated by the DNA methylation of DNMT3A [33]. Prenatal arsenic exposure impacts the fetus and may induce enduring epigenetic alterations in its progeny. Research indicates that prenatal maternal arsenic exposure influences juvenile growth and development by increasing IGFBP3 levels via the methylation of 12 particular CpG loci [34]. Research on animals has demonstrated that maternal arsenic exposure during gestation may directly influence DNA methylation patterns and traits of offspring [35] [36]. Arsenic exposure during gestation led to diminished sperm quality and histopathological abnormalities in F0 generation mice, while also dramatically decreasing methylation levels of the genes Igf2 DMR2 and H19 DMR in the F1 and F3 generations [37]. Chronic arsenic exposure has been documented to modify DNA methylation and induce DNA mutations in murine testicular mesenchymal cells. A study on arsenic lineage revealed that rats subjected to chronic exposure

to As_2O_3 experienced genotoxic damage (F0-F3) and displayed intergenerational alterations in testicular and ovarian DNA methylation levels [38]. Research has demonstrated that exposure to $NaAsO_2$ during gestation disrupts fetal germ cell development and modifies the DNA methylation of particular transposons, including L1MdA and IAPE, in zygotic sperm [39]. Furthermore, arsenic obstructs DNA methylation pathways, including LINE-1, by depleting the methyl donor SAM, resulting in the increase of LINE-1 expression. The anomalous activation of LINE-1 correlates with sperm damage [40]. Paternal non-occupational arsenic exposure was observed to increase DNA methylation levels of MEG3 in spermatozoa and exhibited a substantial positive correlation with urine arsenic levels [41]. Consequently, prolonged parental arsenic exposure may result in comprehensive alterations in DNA methylation and exhibit transgenerational genotoxic effects, perhaps linked to the emergence of reproductive anomalies [42].

2.3. Roles of DNA Methylation in Arsenic-Induced Toxicity in Other Organs

Prolonged exposure to arsenic is accompanied by significant changes in DNA methylation, which not only can have harmful effects on the liver, kidneys, reproductive system, but also on the skin, cardiovascular system, neurological system, and other bodily organs (**Table 1**). The skin is among the most vulnerable organs to arsenic toxicity in humans, with exposure frequently resulting in aberrant pigmentation, hyperkeratosis, and perhaps skin cancer. Arsenic-exposed skin tissues exhibit general hypomethylation and promoter hypermethylation of particular genes (e.g., p16, p53, MLH1) [43]. A study of three generations of arsenic-exposed patients with skin lesions revealed reduced genome-wide DNA methylation levels in blood cells [44]. Conversely, 183 differentially methylated genes were linked to skin lesions in the peripheral blood leukocytes of arsenic-exposed women, with 182 exhibiting hypermethylation [45]. Research indicates that particular DNA methylation patterns correlate with arsenic exposure from coal combustion. For instance, hypermethylation of DNA at p15INK4b, ERCC1, and ERCC2 correlates with skin cancer generated by arsenic from coal burning [44]. Furthermore, the methylation levels of specific CpG sites in the RPL34, SERPINA9, and DUT genes were markedly increased in a population at skin cancer due to arsenic exposure. This suggests that these sites could serve as potential molecular markers for arsenic exposure and skin cancer risk [46]. Epidemiological research indicates that exposure to hazardous metals, such as arsenic, correlates with cognitive impairment, with DNA methylation potentially playing a crucial role in this relationship. Arsenic exposure leading to DNA hypomethylation in the cerebral cortex, which correlates with memory deficits [47]. Research on individuals exposed to arsenic has revealed 73 CpG loci correlated with blood arsenic concentrations, including two loci, cg05226051 in TDRD3 and cg18886932 in GAL3ST3, linked to cognitive deterioration [48].

Research indicates that aberrant DNA methylation alterations may correlate

with atherosclerotic cardiovascular disease (CVD) occurrences [49]. Schmidt *et al*. that identified modified methylation areas and gene locations in mice with arsenic-induced atherosclerosis [49]. A survey of American Indians with chronic arsenic exposure revealed that variations in methylation patterns at particular CpG sites partially elucidated the correlation between arsenic exposure and heart disease risk [50]. Prolonged exposure to arsenic-laden drinking water has been linked to a higher prevalence of diabetes. Research indicates that exposure to $NaAsO_2$ can alter the methylation levels of CpG sites (-1743 and -1734) within the promoter region of the key gene (Glut2) involved in insulin metabolism. This could result in compromised islet function [15]. Inorganic arsenic is converted *in vivo* by methylation into comparatively less hazardous organic derivatives, including monomethyl arsenic (MMA), dimethyl arsenic (DMA), and trimethyl arsenic (TMA) [51]. DMA^V has been shown to develop bladder epithelial carcinoma (UC) in rats consuming water containing DMA^V [52]. In DMA^V-induced UC in rats, 40 genes that were highly methylated and down-regulated were found, including CPXM1, OPCML, TBX20, and KCND3 [53]. Likewise, diminished expression occurred due to hypermethylation of the p16 and death-associated protein kinase (DAPK) promoters in urinary tract epithelial tumors from individuals exposed to arsenic [54]. A study of $NaAsO_2$-treated SV-HUC1 cells demonstrated increased DNA methylation levels of the WIF1 gene in bladder cancer [55]. Population-based bladder cancer studies have revealed markedly elevated methylation levels at the promoter sites of RASSF1A and PRSS3 [55]. Consequently, DNA methylation is pivotal in arsenic-induced bladder carcinogenesis.

Table 1. Role of DNA methylation in arsenic toxicity.

Research objects	Arsenic compounds	Poisoning methods	Poisoning duration	Mechanisms of toxicity	Refs
Mice	5 mg/kg $NaAsO_2$	Gastric gavage	6 or 24 hours	There were differences in DNMTs and genome-wide DNA methylation levels between different types of mice	[20]
L-O2 cells	0.2 μM As_2O_3	-	48 hours	High DNA methylation in the promoter regions of genes such as ERCC2, RPA1, c-MYC, and WNT2B	[21]
LX-2 cells	0, 5, 10, 15 μmol/L $NaAsO_2$	-	24 hours	High methylation of the promoter regions of the ferroptosis-related genes SLC7A11 and CDKN1A	[22]
HepG2 cells	0.5 μM-50 μM $NaAsO_2$	-	24 hours or 10, 20 days	Overall hypomethylation	[23]
Mice	1, 10, 245, 2300 ppb arsenic	Drinking water	Two weeks before pregnancy until the birth of F1 mice	Differential methylated CpG sites and dysregulation of differential methylated regions	[24]
HK-2 cells	100 pg/ml, 10 ng/ml $NaAsO_2$	-	72 hours	Changes in DNA methylation-related enzymes	[27]
Human	-	-	Prenatal arsenic exposure	Decreased DNA methylation at specific CpG sites of the C18ORF8 gene	[31]

Continued

Mice	85 ppm $NaAsO_2$	Drinking water	from days 8 to 18 of pregnancy	The methylation levels of the imprinting genes Igf2 DMR2 and H19 DMR have decreased	[37]
Rat	1 ppm As_2O_3	Drinking water	16 weeks	Generational change in sex gland DNA methylation	[38]
Rat	0.01, 10 mg/L $NaAsO_2$	Drinking water	30 days	Alter the DNA methylation of specific transposons L1MdA and IAPE	[39]
Human	-	Coal burning	-	DNA hypermethylation in the promoter regions of the p15INK4b, ERCC1 and ERCC2 genes	[44]
Human	-	Drinking water	-	Hypermethylation	[45]
Human	-	Drinking water	-	The methylation levels of specific CpG sites in the RPL34, SERPINA9 and DUT genes have increased	[46]
Human	-	Drinking water	-	Changes in the TDRD3 and GAL3ST3 CpG sites	[48]
SV-HUC-1 cells	2 4, 10 μm $NaAsO_2$	-	48 hours	High methylation of the DAPK gene	[54]
Mice	50 ppm $NaAsO_2$	Drinking water	2 weeks	The DNA methylation level in the promoter region of the WIF1 gene has increased	[55]

3. Roles of ncRNAs in Arsenic Toxicity

NcRNAs are RNA molecules that do not encode proteins and comprise more than 90% of the RNA found in the human genome [56]. NcRNAs are categorized based on their length, structure, and location, with miRNAs, lncRNAs, and circRNAs being the most intensively researched [57]. NcRNAs are generally recognized for their ability to interact with diverse proteins, DNA, and other RNAs, hence influencing the activities of these targets and regulating several biological processes [58]. Recent investigations have demonstrated that miRNAs, lncRNAs, and circRNAs are implicated in arsenic poisoning [58].

3.1. Roles of miRNAs in Arsenic Toxicity

miRNAs are a category of brief, non-coding, endogenous RNA molecules that modulate gene expression by interacting with the 3' untranslated region (3'-UTR) of target mRNAs. This interaction results in translational repression or mRNA degradation, hence regulating gene expression at the post-transcriptional stage. MiRNAs participate in various biological processes, encompassing cell development, proliferation, and death [59]. Arsenic and its compounds are known to be toxic to various organs, including the kidneys, skin, and liver, with toxicity linked to dysregulation of different miRNAs, suggesting that miRNAs could function as potential biological markers for the prevention, diagnosis, and treatment of arsenic toxicity [19].

3.1.1. Roles of miRNAs in Arsenic-Induced Hepatorenal Toxicity

Numerous miRNAs have been documented to participate in arsenic-induced toxicity through intricate processes (**Figure 1**). In $NaAsO_2$-treated rats, arsenic was observed to modulate the expression of miR-155, Dicer1, and SOD1 through AUF1, instigating oxidative stress that results in liver damage. Moreover, miR-155 released by $NaAsO_2$-transformed L-02 cells can be conveyed to adjacent cells, instigating an inflammatory response [60]. The impact of arsenic on the liver also implicates the Nrf2 pathway. Balaji et al discovered that arsenic modulates autophagy and apoptosis-related proteins, affecting Nrf2/HO-1/Sirt1/miR-34a levels and enhancing autophagy in the liver [61]. miR-21 is implicated in numerous fibrotic diseases. $NaAsO_2$ promotes the induction of miR-21 in L-02 cells via activating the EPK signaling pathway through PTEN, resulting in cellular autophagy [62]. miR-21 may potentially modulate M2 polarization or the HIF-1*α*/VEGF signaling pathway in macrophages, which is implicated in arsenic-induced liver fibrosis [63]. Moreover, miR-191 expression was seen to be increased in the livers of $NaAsO_2$-treated animals, potentially mediating arsenic-induced hepatic insulin resistance through the insulin receptor substrate 1 (IRS1)/protein kinase B (AKT) pathway by disrupting glucose transport protein 4 (GLUT4) function [64]. miR-1294 was markedly upregulated in arsenic trioxide-treated hepatocellular carcinoma (HCC) cells, targeting TEAD1/PIM1 to trigger apoptosis [65]. Exposure to arsenic triggers cellular pyroptosis, resulting in hepatotoxicity. Treatment with $NaAsO_2$ enhances the expression of miR-150-5p in human hepatic stellate cells (LX-2). This subsequently influences the SOCS1 and NF-*κ*B/NLRP3 pathways, intensifying cellular pyroptosis [66]. Prior research has demonstrated that As_2O_3 can induce changes in renal morphology, such as tubular dilatation and glomerular congestion. Research on populations exposed to arsenic has demonstrated that miR-21 and miR-145 correlate with hepatic injury, while miR-191 is significantly linked to renal impairment [67]. miRNA 181a-5b is a mitochondrial microRNA produced in the kidney that targets the cytochrome c1 gene (CYC1) and augments inflammatory response functionality. The research findings indicate that the overexpression of miR-181 expression in As_2O_3-treated rats correlates with renal injury [68]. A study including adolescents demonstrated a negative correlation between urine arsenic content and the expression of miR-21 and miR-221, microRNAs potentially implicated in the pathogenesis of arsenic-induced proteinuria [69]. A research of arsenic-exposed miners revealed a correlation between peripheral blood levels of miR-155 and miR-200b and urine arsenic metabolites, with miR-200b levels indicating increased quantities of urinary arsenic metabolites [70]. Prior research has demonstrated that arsenic exposure aggravates renal damage in diabetic nephropathy (DN) rats. In diabetic nephropathy mice, persistent treatment of $NaAsO_2$ modified autophagy and intensified the course of diabetic nephropathy. The miRNA-mRNA axis comprising let-7a-1-3p, let-7b-3p, let-7f-1-3p, miR-98-3p/Cdc42, Mapk1, and Rhoa is considered a crucial pathway in the process of diabetic nephropathy development due to excessive arsenic exposure [71].

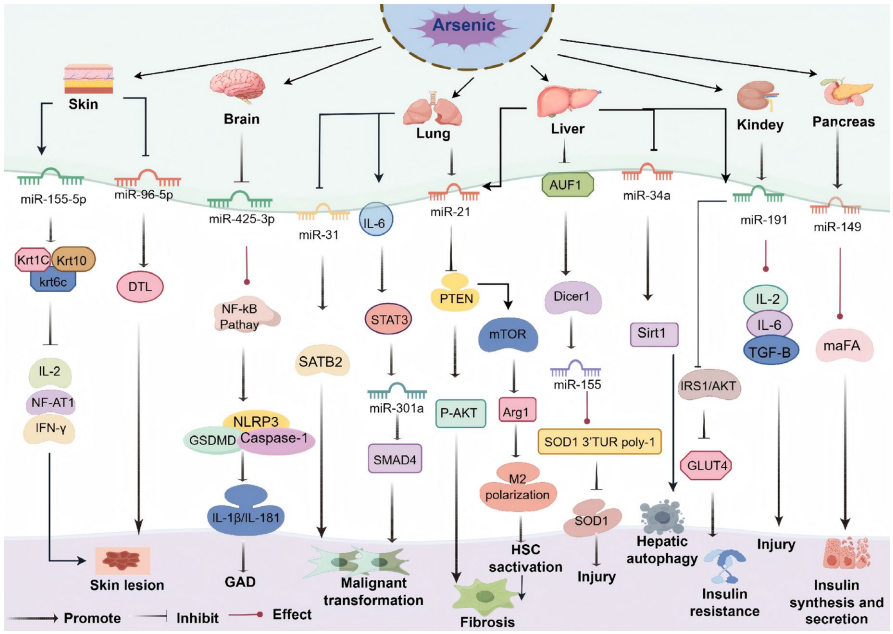

Figure 1. The mechanism of miRNAs in arsenic-induced toxicity to various organs. Arsenic toxicity and miRNA expression in skin, brain, lung, liver, kidney, pancreas and other organs caused by different pathways ultimately lead to organ damage, fibrosis, malignant transformation, GAD and insulin resistance.

3.1.2. Roles of miRNAs in Arsenic-Induced Reproductive Toxicity

Exposure to arsenic during gestation might hinder fetal growth, elevate the likelihood of spontaneous abortion, and result in various health complications [72]. Northern Mexico impacts a significant population due to elevated arsenic concentrations in drinking water (>50 μg/L). A comprehensive miRNA analysis of neonatal umbilical cord blood revealed 12 miRNAs correlated with maternal urinary arsenic concentrations, with miR-107 and miR-20b linked to the beginning of diabetes [73]. In $NaAsO_2$-exposed pregnant mice, hepatic expression of several miRNAs was altered, exhibiting increased levels of miR-205, miR-203, miR-215, and miR-34a, alongside decreased levels of miR-217 [74]. In a similar vein, Chen *et al.* examined the livers of arsenic-exposed mice across various developmental stages (spermatogenesis, gestation, and lactation) and discovered 86 differentially expressed miRNAs, with miR-192-5p and miR-21a-5p significantly upregulated, while miR-7083-5p and miR-7052-5p were significantly downregulated [75]. microRNAs can be conveyed via extracellular vesicles and particles (EVPs), which are crucial for maternal-offspring contact and the healthy development of the kid. The study indicated that arsenic exposure during pregnancy and prenatally correlated with the total miRNA content of breast milk extracellular vesicles in a birth cohort, revealing 13 miRNAs adversely connected with arsenic exposure [76]. Research on miRNA expression in arsenic-induced prostate cancer is scarce. The expression of nine miRNAs was markedly diminished in As-CSCs cells subjected to prolonged arsenic exposure. Specifically, miR-143 may serve as a potential diagnostic and therapeutic target for arsenic-induced prostate cancer [77]. None-

theless, miR-34a, let-29b, miR-193b, and miR-7 are known to be upregulated in arsenic-transformed prostate stem cells (As-CSCs) and epithelial cells [74].

3.1.3. Roles of miRNAs in Arsenic-Induced Toxicity in Other Organs

In West Bengal, India, miR-21 and miR-155-5p were enhanced in patients with chronic arsenic exposure resulting from groundwater contamination in individuals with skin impairments [78]. Research indicates that miR-21 participates in the NaAsO2-induced malignant transformation of HaCaT cells and Epithelial-Mesenchymal Transition (EMT) via the IL-6/STAT3 pathway [79]. Conversely, miR-96-5p levels were markedly diminished to modulate DTL and facilitate transformation in HaCaT cells induced by $NaAsO_2$ [80]. The malignant transformation of arsenic-treated HaCaT cells was also linked to miR-141 and miR-200a. A case-control study with elevated arsenic exposure demonstrated that miR-663 expression levels were considerably diminished in malignant tissues compared to non-cancerous tissues [81]. miRNAs are implicated in the modulation of heavy metals' effects on cerebral function. For instance, miR-124 mitigates arsenic toxicity in nerve cells, inhibit endoplasmic reticulum stress, and is significantly correlated with neurocognitive development in children [67]. The expression of miR-219 is influenced by neurotoxic agents such as arsenic. Research indicates that miR-219 targets calpain II and modulates $NaAsO_2$-induced structural damage in the hippocampus, as well as learning and memory deficits [82]. Moreover, inorganic arsenic decreased miR-425-3p levels in rats treated with $NaAsO_2$. miRNA promotes the NLRP3/Caspase-1/GSDMD pathway by targeting NF-κB signaling molecules, resulting in the release of IL-1β and IL-18, which induces neuronal cell death and exacerbates generalized anxiety disorder (GAD) [83].

The lung is a significant target organ for arsenic toxicity, and arsenic is intricately linked to the onset of several pulmonary illnesses. Research indicates that the overexpression of miR-195-5p is involved in the cytotoxic effect of $NaAsO_2$ treatment on human normal bronchial epithelial (BEAS-2B) cells [84]. It was similarly discovered that the overexpression of miR-301a, reliant on the IL-6/STAT3/miR-301a/SMAD4 signaling pathway, contributes to arsenic-induced transformation of BEAS-2B cells [85]. Moreover, arsenic exposure diminishes miR-31 expression, thereby modulates the AT sequence-rich binding protein 2 (SATB2), resulting in malignant cellular transformation [86]. Prolonged exposure of BEAS-2B cells to low levels of As^{3+} (250 nM) led to the regulation of miR-21 on PTEN via AKT activation and enhanced glycolysis, correlating with myofibroblast differentiation and lung fibrosis [87]. Changes in miRNAs generated by arsenic exposure have been documented to aggravate cardiotoxicity. As_2O_3 markedly augmented the function of miRNAs in QT interval prolonging. miR-423-5p and miR-454-5p were correlated with arsenic metabolites in the plasma of individuals from regions with elevated arsenic concentrations in Mexico, and these miRNAs were linked to cardiovascular disease [88]. Moreover, it was demonstrated that miR-155, miR-126, and CVD were substantially correlated. Consequently, miR-126-3p has been recognized as an early biomarker for CVD [89]. miRNAs provide a post-

transcriptional regulatory function in preserving normal pancreatic β-cell activity and in the etiology of type 2 diabetes (T2D). Exposure to $NaAsO_2$ markedly altered the expression of ten miRNAs in pancreatic β-cells (INS1832/13), with four being upregulated and six down-regulated [90]. miR-149 was upregulated in Min6 cells as a result of diminished insulin secretion following $NaAsO_2$ exposure, indicating the role of miRNAs in arsenic-induced pancreatic toxicity [77]. Moreover, miR-181a-3p-irs2, miR-181a-3p-sirt1, and others may contribute to the onset of insulin resistance in diabetic mice subjected to elevated arsenic exposure [91]. The miR-200 family has been shown to exhibit diminished expression in various cancer forms, including urothelial carcinoma. It was observed that miR-200a/b/c, and miR-205 were diminished in the urine of individuals exposed to arsenic [92]. Therefore, arsenic alters the expression patterns of miRNAs, thereby influencing the *in vitro* and *in vivo* toxic processes it induces (**Table 2**).

Table 2. Role of miRNAs in arsenic toxicity.

Research object	Tissues or cells	Arsenic compounds	Doses	Poisoning methods	Poisoning times	Trends of miRNAs	Mechanisms of toxicity	Refs
Rat	Liver tissue	$NaAsO_2$	0, 25, 50, 100 mg/L	Drinking water	24 weeks	miR-155 ↑	miR-155 inhibits SOD1 protein expression by acting on the 3'UTR region of SOD1, leading to liver injury	[60]
Rat	Hepatocytes	$NaAsO_2$	15 mg/kg	orally	28 days	miR-34a ↓	Arsenic regulates the levels of Nrf2/HO-1/Sirt1/miR-34a, leading to hepatic autophagy	[61]
Mice	Liver tissue	$NaAsO_2$	0, 10 or 20 ppm	Drinking water	0, 3, 6, 12 months	miR-21 ↑	miR-21 promotes arsenic-induced liver fibrosis by regulating the HIF-1α/VEGF signaling pathway	[63]
Mice	Liver tissue	$NaAsO_2$	0, 20 ppm	Drinking water	12 months	miR-191 ↑	miR-191 participates in hepatic insulin resistance by inhibiting the IRS1/AKT pathway	[64]
Human	LX-2 cells	$NaAsO_2$	10 μmol/L	-	24 hours	miR-150-5p ↑	Arsenic promotes pyroptosis of cells through the miR-150-5p/SOCS1/NF-κB/NLRP3 pathway	[66]
Human	Urine	Arsenic	27.85 μg/L	Coal burning	-	miR-191↑	miR-191 regulates inflammatory factors such as IL-2, IL-6, and TGF-β, and plays a role in renal dysfunction	[67]
Human	Urine	Arsenic	0.0076 mg/m^3	Occupational exposure	3 months	miR-200b ↑	miR-200b regulates arsenic-related metabolites involved in renal dysfunction	[70]
Human	Urine	$NaAsO_2$	10, 25 mg/L	-	14 weeks	(let-7a-1-3p let-7b-3p let-7f-1-3p miR-98-3p) ↓	Arsenic exposure leads to renal fibrosis, through the miRNA-mRNA axis	[71]
Human	Skin tissue	Arsenic	-	-	-	miR-155-5p ↑	miR-155-5p regulatory proteins and factors are involved in arsenic toxicity	[78]
Human	HacaT cells	$NaAsO_2$	0.1 μmol/L	-	3 or 7 weeks	miR-96-5p ↓	miR-96-5p up-regulate DTL, leading to proliferation and malignant transformation of HaCaT cells	[80]
Rat	Brain tissue	$NaAsO_2$	50, 100 μg/L	Drinking water	21 days	miR-425-3p ↓	miR-425-3p regulates NF-κB to cause neuronal pyroptosis and promotes the onset of GAD	[83]
Human	BEAS-2B cells	As_2O_3	0.25 μM	-	6 months	miR-301a ↑	The IL-6/STAT3/miR-301a/SMAD4 cascade promotes arsenic-induced cell transformation	[85]
Human	BEAS-2B cells	$NaAsO_2$	2 μM	-	6 weeks	miR-31 ↓	Arsenic through the miR-31/SATB2 pathway, leads to malignant transformation of cells	[86]
Mice	Lung tissue	$NaAsO_2$	0, 5, 10, 20 ppm	Drinking water	6 months	miR-21 ↑	miR-21 induces pulmonary fibrosis through the PTEN/P-AKT pathway	[87]
Human	Heart	Arsenic	>10 μg/L	-	-	miR-155 ↑ miR-126 ↓	There was a signif1icant association between As levels and serum expression levels of miR-155 and miR-126	[89]

Note: The symbols of ↑or ↓indicate the upregulation or downregulation of miRNAs.

3.2. Roles of lncRNAs in Arsenic Toxicity

LncRNAs are a category of ncRNA molecules exceeding 200 nucleotides in length [93]. LncRNAs have been demonstrated to participate in several cellular activities, including proliferation, apoptosis, and migration, as well as in arsenic-induced toxicological reactions [94]. Consequently, modified lncRNA expression profiles are intricately linked to arsenic-induced toxic damage (**Table 3**).

3.2.1. Roles of lncRNAs in Arsenic-Induced Hepatorenal Toxicity

Arsenic exposure has been demonstrated to alter the expression of many lncRNAs and is implicated in liver damage, fibrosis, and hepatocellular cancer. Fibrosis-associated lncRNA H19, HOTAIR, and MALAT1 were increased in the livers of arsenic-exposed mice [95]. $NaAsO_2$-stimulated HCC tissues exhibited elevated expression levels of both hypoxia-inducible factor-2α (HIF-2α) and MALAT1, synergistically enhancing the cell invasion and metastasis ability. Furthermore, the buildup of HIF-2α may facilitate aberrant cell proliferation by influencing the expression of cell cycle-associated proteins (e.g., p21) [96]. In L-02 cells treated with $NaAsO_2$, MALAT1 can infiltrate LX-2 cells by exosomes. It also participates in liver fibrosis by modulating the miRNA-26b/COL1A2 pathway [97]. Another HOTAIR situated at the HOXC locus, arsenic exposure, facilitates $NaAsO_2$-induced liver fibrosis via the HOTAIR/RORγt/miR-17-5p/IL-17 pathway [98]. Arsenic exposure severely impacted hepatic lipid metabolism. $NaAsO_2$ elevated the antisense RNA of the proto-oncogene PU.1 (lncRNA PU.1 AS) in murine liver. By regulating the expression of Zeste chromosomal enhancer homologous protein 2 (EZH2)/Sirtuin 6 (Sirt6)/sterol regulatory element-binding protein-1c (SREBP-1c), thereby influencing triglyceride synthesis [62]. lncRNA UCA1, a significant epigenetic regulator associated with cancer, interacts with EZH2 to modulate NFATc2, therefore mitigating cell cycle arrest in arsenic-induced hepatotoxicity [99]. MEG3 is a long non-coding RNA situated on chromosome 14, playing a role in the regulation of the cell cycle, apoptosis, proliferation, and autophagy [100]. MEG3 and PKM2 can affect As_2O_3-induced epithelial-mesenchymal transition in hepatocellular cancer [100]. Moreover, arsenic exposure elevated the expression of lncRNA PANADR, HOTAIR, and LincRNA-p21, correlating with variations in urine arsenic levels across workers [101].

3.2.2. Roles of lncRNAs in Arsenic-Induced Reproductive Toxicity

Research on animals has shown that arsenic accumulates in the testes, causing damage to sperm DNA, which subsequently hinders male reproductive function and elevates the chance of infertility [102]. NcRNAs are essential regulators of gene expression and epigenetic processes during spermatogenesis. Growth arrest-specific 5 (Gas5), a lncRNA, is implicated in multiple biological processes, such as cell cycle regulation, growth arrest, and apoptosis. Prenatal exposure to arsenic (50 ppb) has been demonstrated to modify the expression of the glucocorticoid receptor (GR) and Gas5 in the developing murine brain, potentially resulting in outcomes such as learning disabilities, memory impairments, heightened depres-

sive-like behaviors, and enduring changes in the set point of GR feedback. Decreased nuclear GR levels were seen in male mice at all gestational time points examined, whereas no alterations were observed in female mice. Additionally, total cellular Gas5 levels were reduced in arsenic-exposed male mice, but no alterations in Gas5 levels were seen in arsenic-exposed female mice during gestation days 16 to 18. The data indicate that arsenic exposure in male mice may affect GR levels in the brain's telencephalon by modulating Gas5 levels [103].

3.2.3. Roles of lncRNAs in Arsenic-Induced Toxicity in Other Organs

LncRNAs have been identified as pivotal in brain development, neuronal differentiation, survival, and regeneration. In the hippocampus tissues of rats exposed to $NaAsO_2$, 177 differently expressed lncRNA molecules were discovered. These lncRNAs exhibited high enrichment in neurodegenerative processes, Huntington's disease, and several pathways associated with nerve injury. Research indicated that arsenic can induce nerve damage in rats via the lncRNA-ENSRNOT00000022622/miR-206-3p/Bdnf pathway [104]. The research has found that H19, associated with lung cancer and lung fibrosis. $NaAsO_2$ reduced let-7a by modulating H19, c-Myc, and Arg1, resulting in lung fibrosis in mice [105].

LncRNAs demonstrate various regulation mechanisms in arsenic-induced apoptosis. for example, MEG3 modulates inorganic arsenic-induced apoptosis in A549 cells by up-regulating pro-apoptotic genes, including CASP7, CCND3, and APAF1, while down-regulating anti-apoptotic proteins, such as BCL2A1 and apoptosis inhibitory factor 5 (API5) [106]. The recently discovered lncRNA- Alu-mediated p21 transcriptional regulator (APTR), also affects arsenic-induced apoptosis and proliferation inhibition. All transcripts of APTR and transcript NR_134251.1 exhibited a dose-dependent increase in $NaAsO_2$-treated 16HBE cells [107]. Likewise, TUG1, as is a lncRNA that modulates cellular proliferation, is elevated in arsenic-exposed individuals. Arsenic promotes apoptosis in HBE cells by upregulating TUG1 through the activation of the p53 signaling pathway [108]. The reprogramming regulator (linc-ROR) is a lncRNA situated on chromosome 18q21.31. Following the treatment of HBE cells with $NaAsO_2$ for 40 generations, The linc-ROR was activated through the regulation of nuclear transcription factor 2 (Nrf2), collaboratively participate in arsenic-induced carcinogenesis and progression [109]. Research report, arsenic promotes the expression of programmed cell death ligand one (PD-L1), suppresses T cell effector function, and facilitates lung tumor development in mice. Subsequent investigations demonstrated that lnc-DC collaborated with STAT3 to augment the elevation of PD-L1 expression in $NaAsO_2$-induced malignant transformation of BEAS-2B cells [110].

Kcnq1ot1 is a lncRNA that is essential for cardiac development and is linked to arsenic-induced myocardial damage. Research has demonstrated that the lncRNA Kcnq1ot1/miR-34a-5p/Sirt1 pathway plays a crucial role in As_2O_3-induced cardiomyocyte apoptosis [111]. However, Long non-coding RNA nuclear-enriched transcript 1 (NEAT1) promotes As_2O_3-induced damage in H9c2 cells via the miR-

124/NF-kB signaling pathway [112]. The lncRNA DICER1-AS1 is an antisense transcript of DICER1, functioning as a ribonuclease and regulating gene expression. $NaAsO_2$ treatment of A549 cells was demonstrated to downregulate DICER1-AS1, thereby modulating the cell cycle and suppressing cell growth. Likewise, As_2O_3 can impede breast cancer cell proliferation by downregulating DICER1-AS1 [113]. Consequently, lncRNAs are pivotal in modulating cancer cell proliferation, apoptosis, and metastasis. As_2O_3 was discovered to activate the lncRNA ovarian tumor domain containing 6B antisense RNA1 (lncRNA OTUD6B-AS1) through ROS-mediated MTF1. lncRNA OTUD6B-AS1 through the modulation of miR-6734-5p and mitochondrial NADP+-dependent isocitrate dehydrogenase 2 (IDH2), hence amplifying As_2O_3-induced cytotoxicity in T24 cells (a human bladder cancer cell line) [114]. **Figure 2** presents the regulatory mechanisms of lncRNA in the arsenic-induced toxicity of various organs.

Table 3. Role of lncRNAs in arsenic toxicity.

Research object	Tissues or cells	Arsenic compounds	Doses	Poisoning methods	Poisoning duration	Trends of lncRNAs	Mechanisms of toxicity	Refs
Human	L-02 cells	$NaAsO_2$	2.0 μM	-	3, 6, 12, 24 hours	MALAT1 ↑	HIF-2*α* and MALAT1 jointly enhance the invasive and metastatic abilities of cells	[96]
Mice	Hepatic tissue	$NaAsO_2$	20 ppm	Drinking water	9 months	HOTAIR ↑	HOTAIR down-regulates miR-17-5p thereby activating HSC to promote liver fibrosis	[98]
Mice	Hepatic tissue	$NaAsO_2$	50 mg/L	Drinking water	5 weeks	lncRNA PU.1 AS ↑	lncRNA PU.1 AS/EZH2/Sirt6/SREBP-1c pathway, affects the synthesis of triglycerides	[62]
Human	L-02 cells	As_2O_3	5 mmol	-	24 hours	MEG3 ↑	Arsenic regulates MEG3, and PKM2 inhibits EMT	[100]
Rat	Hippocampal tissues	$NaAsO_2$	0, 2, 10, 50 mg/L	Drinking water	12 weeks	lncRNA-ENSRNOT-00022622 ↓	Arsenic may participate in rat neurological injury through the ENSRNOT000000226-22/miR-206-3p/Bdnf axis	[104]
Mice	Lung tissues	$NaAsO_2$	0, 10, 20 ppm	Drinking water	12 months	H19 ↑	Arsenic through the H19/c-Myc/Arg1/let-7a signaling pathway, leads to liver fibrosis	[105]
Human	A549 cells	Arsenic	30, 60, 90 μmol/L	-	48 hours	MEG3 ↑	MEG3 regulates apoptosis by regulating downstream target genes	[106]
Human	HBE, A549 cells	$NaAsO_2$	2.5 μmol/L	-	24 hours	linc-ROR ↑	Linc-ROR and Nrf2 jointly participate in the process of arsenic-induced lung tumors	[109]
Mice	Cardiomyocytes	As_2O_3	2.5, 5 μM	-	48 hours	lncRNA *Kcnq1ot1* ↓	Arsenic promotes cell apoptosis through the lncRNA Kcnq1ot1/miR-34a-5p/Sirt1 signaling pathway	[111]
Rat	H9c2 cells	As_2O_3	10 μM	-	24 hours	lncRNA NEATI↓	Arsenic promotes cell damage through the lncRNA NEAT1/miRNA-124/NF-*κ*B pathway	[112]
Human	A549 cells	$NaAsO_2$	0, 20, 40, 60 μmol/L	-	48 hours	lncRNA DICER1-AS1↓	lncRNA DICER1-AS1 can inhibitthe proliferation of cells	[113]
Human	T24 cells	As_2O_3	10, 20 μmol/L	-	6 hours	lncRNA OTUD6B-AS1 ↑	As_2O_3 enhances cytotoxicity through the MTF1/lncRNA OTUD6B-AS1/miR-6734-5p/IDH2 pathway	[114]

Note: The symbols of ↑ or ↓ indicate the upregulation or downregulation of lncRNAs.

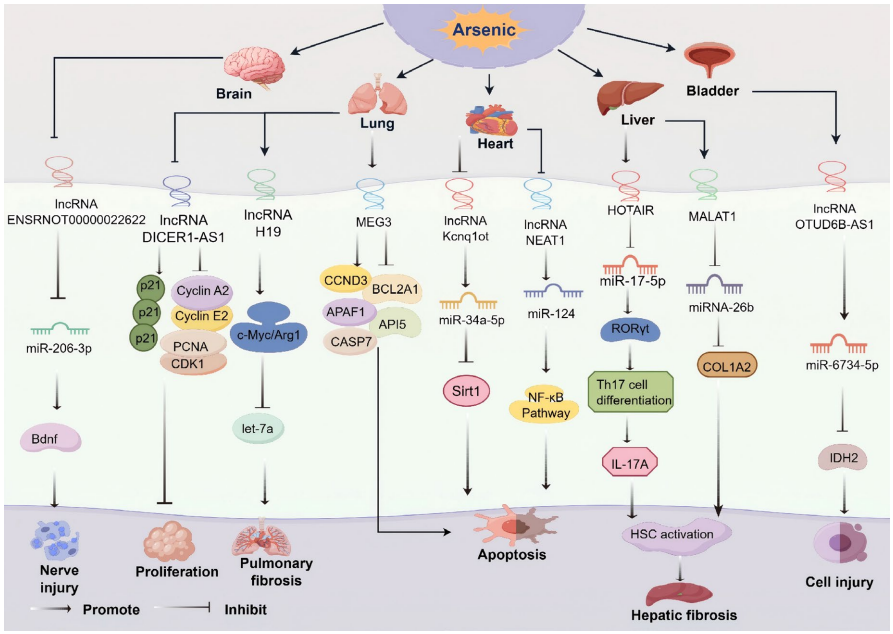

Figure 2. The mechanism of lncRNAs in arsenic-induced toxicity to various organs. lncRNA is involved in arsenic-induced toxicity of nerve, lung, heart, liver, bladder and other organs through different pathways, as well as lncRNA expression, which ultimately leads to organ injury, apoptosis, proliferation, fibrosis.

3.3. Roles of circRNAs in Arsenic Toxicity

circRNAs are a novel category of ncRNAs that are gradually gaining prominence in epigenetic regulation studies. They are generated through reverse splicing of precursor mRNAs (pre-mRNAs) and possess a distinctive covalently closed loop structure, with their 3' and 5' ends interconnected by phosphodiester linkages [115]. In contrast to linear RNAs, circRNAs have significant stability and resistance to breakdown by nucleic acid exonucleases, leading to an extended half-life within the cells [116]. circRNAs possess roles that extend well beyond their initial characterization as mere "splicing by-products". They are extensively engaged in the regulation of biological processes like the cell cycle, cell differentiation, and apoptosis [117]. circRNAs employ multiple methods of action, the most traditional being their function as "miRNA sponges," which impede the regulation of target genes by binding to miRNAs, hence indirectly enhancing gene expression. circRNAs may directly interact with RNA-binding proteins (RBPs) to regulate gene transcription and splicing, and some circRNAs may function as templates for protein translation [118].

Roles of circRNAs in Arsenic-Induced Various Organs Toxicity

The research has found that numerous circRNAs have been recognized as potential biomarkers and modulators of diverse functions in various cells and tissues (**Table 4**). circMTO1, a tissue-specific circRNA, functions as a miR-9 "sponge" in HCC, enhancing the production of the oncogene p21 and thereby impeding hepatocellular carcinoma (HCC) progression [119]. Recent findings indicate that prolonged

arsenic exposure can facilitate the malignant transformation of normal cells through the regulation of circRNAs. Arsenic activates circ100284 in L-02 and HaCaT cells, functioning as a sponge for miR-217 and promoting the cell cycle by upregulating Cyclin D1 and CDK4 through EZH2, resulting in aberrant proliferation and malignant transformation [120]. In arsenic-treated SV-HUC-1 cells, circ100284 activates Aurora kinase B through the miR-217/HSP70 methylation pathway, hence enhancing bladder cancer cell proliferation [121]. Furthermore, arsenic-induced upregulation of circLRP6 expression in HaCaT cells, along with circLRP6's binding to miR-455, resulted in the upregulation of Zinc Finger E Box Binding Homology Box Protein 1 (ZEB1), hence facilitating the EMT process in the cells [122]. Arsenic exposure downregulates circ008913, which functions as a miR-889 sponge, prompting cells to adopt cancer stem cell (CSC) characteristics by modulating the expression of DAB2IP/ZEB1 and skin stem cell markers (e.g., K5, CD34), a critical mechanism in arsenic-induced skin carcinogenesis [123]. Prior research indicates that $NaAsO_2$ enhances circP50 expression in A549 cells. The knockdown of circP50 suppresses the phosphorylation and acetylation of the p53 pathway, modulates downstream target genes, and eventually enhances the proliferation of A549 cells [124]. Conversely, in arsenic-induced malignant transformation of BEAS-2B cells, the expression of circBRWD1 was markedly downregulated among numerous dysregulated circRNAs. circBRWD1 modulates the mRNA stability of c-JUN, c-MYC, and CDK6, hence facilitating cell-cycle progression and cellular proliferation, which contributes to lung cancer [125]. Moreover, a notable elevation of hsa_circ_0005050 was detected in populations chronically exposed to arsenic. Knockdown of hsa_circ_0005050 increased $NaAsO_2$-induced cell viability in A549 cells, but it had the contrary impact on 16HBE cells [126].

circRNAs have demonstrated potential involvement in the cardiovascular toxicity of arsenic [127]. A substantial alteration in the expression of numerous circRNAs was observed in mouse myocardial tissues subjected to $NaAsO_2$ treatment, with the up-regulation of mm9_circ_009519 and down-regulation of mm9_circ_016007 [128]. This indicates that circRNA may play a role in arsenic-induced myocardial injury. Furthermore, circRNA-32011 exhibited down-regulation in arsenic-exposed primary cardiomyocytes, and this down-regulation correlated with diminished cardiomyocyte survival and a reduced Bcl-2/Bax ratio, indicating that circRNA-32011 may exert an inhibitory influence on arsenic-induced cardiomyocyte apoptosis [129]. circRNAs, similar to miRNAs and lncRNAs, are garnering increasing attention in breast cancer research. The expression of circDHX34 was elevated following $NaAsO_2$ treatment of hormone-independent breast cancer cells MDA-MB-231. The knockdown of circDHX34 may augment cell proliferation and suppress apoptosis via modulating apoptosis-related genes, including CASP8, CASP9, BCL2, and BCL2L1, indicating that circRNAs can facilitate apoptosis [130]. Moreover, circPDE3B was markedly increased in arsenic-induced bladder carcinogenesis, modulating SOCS1 to activate

Table 4. Role of circRNAs in arsenic toxicity.

Research objects	Tissues or cells	Arsenic compounds	Doses	Poisoning methods	Poisoning duration	Trends of circRNAs	Mechanisms of toxicity	Refs
Human	L-02 cells	$NaAsO_2$	2 μM	-	24 hours	circ100284 ↑	circ100284 upregulates Cyclin D1 and CDK4 through the miR-217/EZH2 axis, promoting malignant transformation of cells	[120]
Human	HaCaT cells	$NaAsO_2$	-	-	48 - 72 hours	circLRP6 ↑	The combination of circLRP6 and miR-455 upregulates ZEB1 and promotes the EMT process of cells	[122]
Human	HaCaT cells	$NaAsO_2$	1.0 μM	-	48-72 hours	circ008913 ↓	circ008913, through the miR-889/DAB2IP/ZEB1 axis, leads to the acquisition of CSC characteristics by the cells	[123]
Human	A549 cells	$NaAsO_2$	20, 40, 60 μmol/L	-	48 hours	circP50 ↑	circP50 leads to apoptosis mainly through p53 pathway	[124]
Human	BEAS-2B cells	$NaAsO_2$	0.75 μM	-	48 hours	circBRWD1 ↓	circBRWD1 regulate of its targeted mRNA, leading to malignant transformation of cells	[125]
Mice	myocardial cells	As_2O_3	10 μmol/L	-	24 hours	circRNA-32011 ↓	circRNA-32011 regulates apoptosis genes Bcl-2 and Bax, Thereby inhibiting apoptosis of cardiomyocytes	[129]
Human	MDA-MB-231 cells	$NaAsO_2$	3, 6 μM	-	72 hours	circDHX34 ↑	circDHX34 promotes apoptosis of cells by regulating apoptosis genes	[130]
Human	SV-HUC-1 cells	$NaAsO_2$	0.5 μM	-	48 hours	circPDE3B ↑	circPDE3B targets STAT3 and NF-κB, accelerating the malignant transformation of cells	[131]
Human	SV-HUC-1 cells	$NaAsO_2$	2 μM	-	24 hours	circ100284 ↑	circ100284 can activate Aurora kinase B by inducing HSP70 methylation through miRNA-217, thereby promoting the proliferation of bladder cancer cells	[121]

Note: The symbols of ↑ or ↓indicate the upregulation or downregulation of circRNAs.

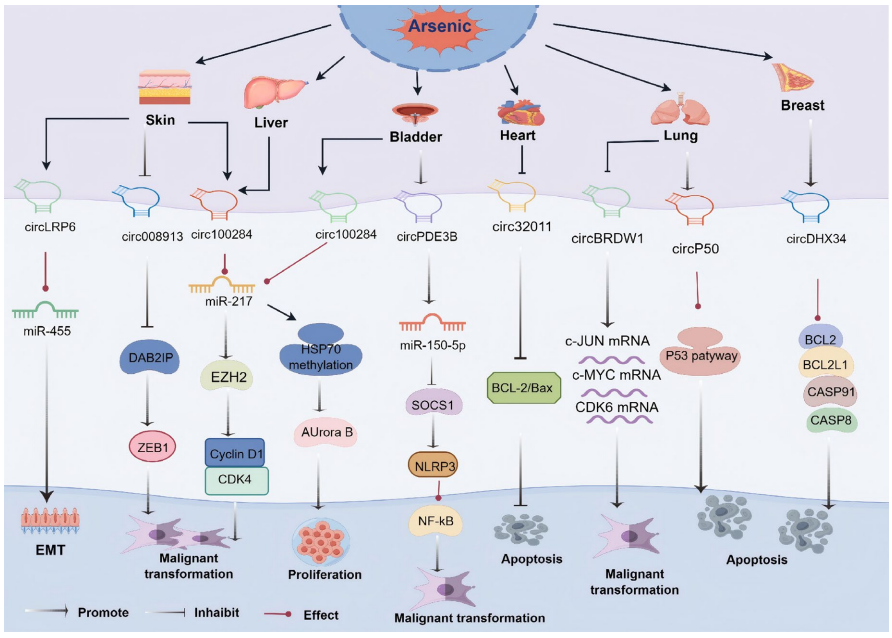

Figure 3. The mechanism of circRNAs in arsenic-induced toxicity to various organs. Arsenic has toxic effects on skin, heart, lung, liver, mammary gland, bladder and other organs through different ways, and eventually leads to malignant transformation, apoptosis, proliferation and so on. circRNA was up-regulated or down-regulated under arsenic treatment.

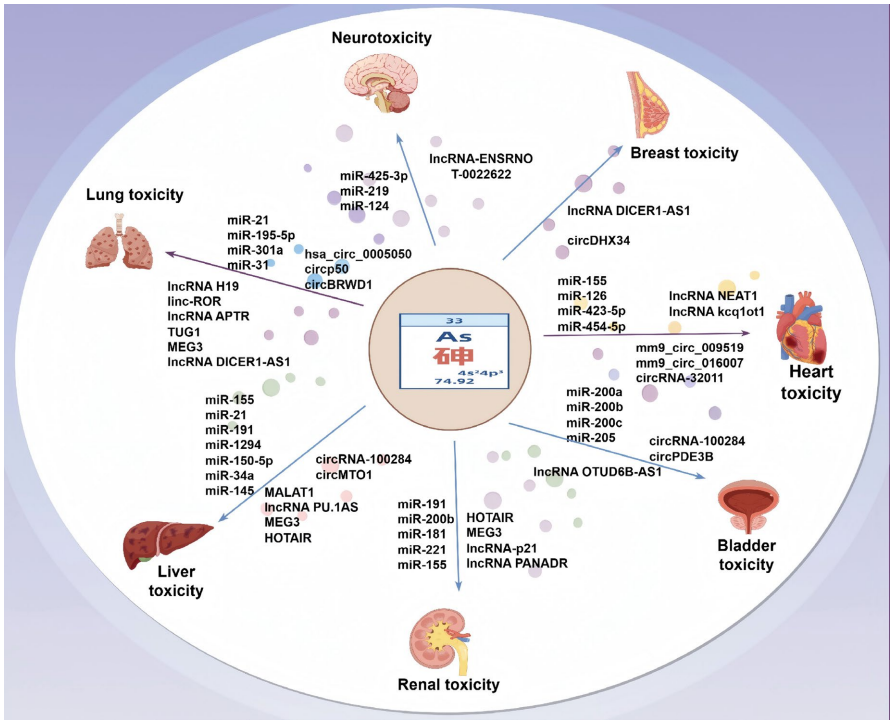

Figure 4. Summary diagram of miRNAs, lncRNAs and circRNAs involved in the toxic effects of arsenic on various organs such as the brain, liver, kidneys, lungs, heart, breast and bladder.

the NF-kB/NLRP3 pathway and expediting the malignant transformation of human bladder epithelial cells [131]. circHIPK3 has been discovered to modulate vascular dysfunction and growth via miRNAs. For instance, As_2O_3 may safeguard rheumatoid arthritis-associated synoviocytes by obstructing the circHIPK3/miR-149-5p/FOXO1/VEGF functional module of angiogenesis [132]. **Figure 3** presents the regulatory mechanism of circRNAs in the arsenic-induced toxicity of various organs. **Figure 4** lists the miRNAs, lncRNAs and circRNAs involved in the toxicity of arsenic to various organs.

4. The Synergistic Role of DNA Methylation and ncRNAs in Arsenic Toxicity

In the investigation of arsenic toxicity mechanisms, DNA methylation and non-coding RNAs do not function separately. Research indicates that alterations in DNA methylation patterns due to arsenic exposure significantly impact the expression profile of miRNAs [133]. Reactive oxygen species (ROS) generated by arsenic metabolism can activate DNMT1, elevate the methylation of the miR-199a-5p gene promoter, activate the miR-199a-5p/HIF-1*α*/COX-2 pathway, and mediate pathological processes including angiogenesis [134]. Furthermore, in arsenic-induced human bronchial epithelial cells, Specific Protein 1 (Sp1) suppresses miR-199a-5p via mechanisms involving DNA methylation and Sp1-mediated transcriptional repression. This inhibition promotes the arsenic-induced

metabolic shift from mitochondrial respiration to PKM2-dependent aerobic glycolysis [133]. Research on uterine arsenic exposure has demonstrated that reduced global DNA methylation correlates with alterations at specific gene loci (e.g., Cyclin D1, Tp53), resulting in substantial modifications in the production levels of certain miRNAs, including miR-205, miR-203, miR-34a, and miR-217. The dysregulated miRNAs are intimately associated with multiple disease processes, including tumorigenesis, pancreatic damage, and diabetes [32]. A study on pregnant mice exposed to arsenic in the placenta confirmed that alterations in DNA methylation are closely associated with the aberrant expression profile of miRNAs in the liver, thereby influencing the target genes of miRNAs and serving as a significant epigenetic mechanism for adverse outcomes induced by arsenic via the placenta [134]. Arsenic exposure drives carcinogenesis by inducing promoter hypermethylation to silence key tumor-suppressive miRNA families. For instance, short-term exposure to sodium arsenite suppresses let-7 family expression via DNAm, thereby disinhibiting the oncogene Ras and activating the NF-κB pathway to facilitate cellular transformation in HaCaT cells [135]. Similarly, in models of chronic arsenic exposure, DNAm-mediated downregulation of the miR-200 family leads to the upregulation of ZEB1, a master regulator that drives EMT and subsequent lung tumorigenesis [136].

Previous studies have strongly demonstrated that DNA methylation in regulatory sequences is associated with changes in the expression of long non-coding RNA genes. Studies have shown that exposure to arsenic can induce PANDAR in workers at arsenic smelting plants, and PANDAR is activated in the arsenic-induced DNA damage response [137]. The methylation of PANDAR is significantly correlated with the inhibition of its RNA expression. LncRNAs and circRNAs can modulate the DNA methylation levels of target genes by direct or indirect interactions with DNMTs or other genes implicated in this mechanism. Nonetheless, it remains ambiguous whether circRNAs may modulate DNA methylation in relation to arsenic toxicity, and the precise process is still not elucidated.

5. Summary and Outlook

Millions globally are persistently exposed to arsenic by the ingestion of contaminated drinking water. The majority of studies have predominantly employed *in vitro* and animal models to investigate the toxicity of arsenic on diverse organ systems which differ from the situation among people in arsenic-contaminated areas. Environmental arsenic exposure, metabolic capacity, age, and food may influence the epigenetic phenotype in individuals. Consequently, extensive research in populations residing in arsenic-contaminated regions should be undertaken to more accurately elucidate the harmful effects. Changes in DNA methylation patterns, a significant form of epigenetic modification, resulting from arsenic exposure may influence gene expression and contribute to the initiation and progression of arsenicosis. The precise mechanism of this process remains unclear, necessitating additional research to elucidate how DNA methylation governs arse-

nic-induced expression of critical genes. NcRNAs (lncRNAs, circRNAs) not only interact with DNA and proteins but also bind to RNAs, particularly miRNAs, hence disrupting critical arsenic toxicity signaling networks. The involvement of other non-coding RNAs, including piRNAs and snRNAs, in arsenic toxicity remains ambiguous. Research increasingly indicates that a complex regulatory network between ncRNAs and DNA methylation, with ncRNAs regulated by epigenetic mechanisms, such as DNA methylation, influencing DNA methylation status. Eevertheless, research on the collaborative effects of lncRNAs, circRNAs, and DNA methylation in relation to arsenic exposure remains nascent, yet their potential significance should not be overlooked. Epigenetic research on arsenic toxicity could uncover novel therapeutic targets and offer innovative treatment techniques for arsenic poisoning and arsenic-related disorders.

Acknowledgements

We sincerely thank the China National Natural Science Foundation and the Yunnan Provincial Science and Technology Department for their financial support. Additionally, we express our heartfelt gratitude to the five participants who voluntarily contributed to the writing and revision of the review.

Funding

This research was supported by grants from the National Natural Science Foundation of China (NO.82260631) to Zuoshun HE and Yunnan Province Basic Research (NO.202301AT070140) to Shiyan GU.

Author Contributions

Jiamin YUAN and Jiao DAI contributed to writing the article, checking the content and sorting out the literature, Rongxian LI, Zuoshun HE, Shiyan GU contributed to reference collection, induction and verification, Shiyan GU revised the manuscript and checking the content of references. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the review, authorship, and publication of this article.

References

[1] Hu, Y., He, J., Ma, Y., Ge, L., Lou, B., Fang, X., *et al*. (2025) Arsenic and Metabolic Diseases: New Insights from Mesenchymal Stem Cells. *Toxicology and Applied Pharmacology*, **498**, Article ID: 117299. https://doi.org/10.1016/j.taap.2025.117299

[2] Ma, M., Zhang, J., Li, S., Zhang, M., Chen, W., Li, L., *et al*. (2024) LINC00942 Alleviates $NaAsO_2$-Induced Apoptosis by Promoting GSH Synthesis through Targeting miR-214-5p. *Biological Trace Element Research*, **203**, 167-177. https://doi.org/10.1007/s12011-024-04167-8

[3] Couto-Santos, F., Guimarães-Ervilha, L.O., Carvalho, R.P.R., Bastos, D.S.S., Souza,

A.C.F., da Silva, R.C., *et al*. (2023) Impact of Early Arsenic Exposure on the Mineral Content and Oxidative Status of the Liver and Kidney of Pubescent and Adult Rats. *Biological Trace Element Research*, **202**, 1644-1655. https://doi.org/10.1007/s12011-023-03787-w

[4] Bibha, K., Akhigbe, T.M., Hamed, M.A. and Akhigbe, R.E. (2023) Metabolic Derangement by Arsenic: A Review of the Mechanisms. *Biological Trace Element Research*, **202**, 1972-1982. https://doi.org/10.1007/s12011-023-03828-4

[5] Koomson, A.A., Delaney, P., Khan, N. and Sadler, K.C. (2024) Sustained Effects of Developmental Exposure to Inorganic Arsenic on Hepatic *gsto*2 Expression and Mating Success in Zebrafish. *Biology Open*, **13**, bio060094. https://doi.org/10.1242/bio.060094

[6] González-Martínez, F., Johnson-Restrepo, B. and Quiñones, L.A. (2024) Arsenic Inorganic Exposure, Metabolism, Genetic Biomarkers and Its Impact on Human Health: A Mini-review. *Toxicology Letters*, **398**, 105-117. https://doi.org/10.1016/j.toxlet.2024.06.008

[7] Rosendo, G.B.O., Ferreira, R.L.U., Aquino, S.L.S., Barbosa, F. and Pedrosa, L.F.C. (2024) Glycemic Changes Related to Arsenic Exposure: An Overview of Animal and Human Studies. *Nutrients*, **16**, Article No. 665. https://doi.org/10.3390/nu16050665

[8] Yang, Y., Li, Y., Li, R. and Wang, Z. (2024) Research Progress on Arsenic, Arsenic-Containing Medicinal Materials, and Arsenic-Containing Preparations: Clinical Application, Pharmacological Effects, and Toxicity. *Frontiers in Pharmacology*, **15**, Article ID: 1338725. https://doi.org/10.3389/fphar.2024.1338725

[9] O'Connor, C., Keele, G.R., Martin, W., Stodola, T., Gatti, D., Hoffman, B.R., *et al*. (2024) Unraveling the Genetics of Arsenic Toxicity with Cellular Morphology QTL. *PLOS Genetics*, **20**, e1011248. https://doi.org/10.1371/journal.pgen.1011248

[10] Sanyal, T., Das, A., Bhattacharjee, S., Gump, B.B., Bendinskas, K. and Bhattacharjee, P. (2024) Targeting the "DNA Methylation Mark": Analysis of Early Epigenetic-Alterations in Children Chronically Exposed to Arsenic. *Science of the Total Environment*, **912**, Article ID: 169049. https://doi.org/10.1016/j.scitotenv.2023.169049

[11] Wadgaonkar, P., Wang, Z. and Chen, F. (2024) Endoplasmic Reticulum Stress Responses and Epigenetic Alterations in Arsenic Carcinogenesis. *Environmental Pollution*, **347**, Article ID: 123565. https://doi.org/10.1016/j.envpol.2024.123565

[12] Rahman, S.U., Liu, X., Khalid, M., Rehman, A., Cao, J., Kayani, S., *et al*. (2024) Beyond Contamination: Enhancing Plant Tolerance to Arsenic through Phytobial Remediation. *South African Journal of Botany*, **164**, 250-265. https://doi.org/10.1016/j.sajb.2023.12.005

[13] Gao, X., Zuo, X., Min, T., Wan, Y., He, Y. and Jiang, B. (2024) Traditional Chinese Medicine for Acute Myelocytic Leukemia Therapy: Exploiting Epigenetic Targets. *Frontiers in Pharmacology*, **15**, Article ID: 1388903. https://doi.org/10.3389/fphar.2024.1388903

[14] Chakraborty, P. and Mukherjee, C. (2024) The Interplay of Metabolic and Epigenetic Players in Disease Development. *Biochemical and Biophysical Research Communications*, **734**, Article ID: 150621. https://doi.org/10.1016/j.bbrc.2024.150621

[15] Stoccoro, A. and Coppedè, F. (2024) Exposure to Metals, Pesticides, and Air Pollutants: Focus on Resulting DNA Methylation Changes in Neurodegenerative Diseases. *Biomolecules*, **14**, Article No. 1366. https://doi.org/10.3390/biom14111366

[16] Bozack, A.K. and Trasande, L. (2024) Prenatal Chemical Exposures and the Methylome: Current Evidence and Opportunities for Environmental Epigenetics. *Epigenomics*,

16, 1443-1451. https://doi.org/10.1080/17501911.2024.2426441

[17] Gu, W., Wang, T., Lin, Y., Wang, Y., Chen, Y., Dai, Y., *et al*. (2024) Particulate Polycyclic Aromatic Hydrocarbons and Metals, DNA Methylation and DNA Methyltransferase among Middle-School Students in China. *Science of the Total Environment*, **926**, Article ID: 172087. https://doi.org/10.1016/j.scitotenv.2024.172087

[18] Shiek, S.S., Sajai, S.T. and Dsouza, H.S. (2022) Arsenic-Induced Toxicity and the Ameliorative Role of Antioxidants and Natural Compounds. *Journal of Biochemical and Molecular Toxicology*, **37**, e23281. https://doi.org/10.1002/jbt.23281

[19] Teschke, R. (2024) Copper, Iron, Cadmium, and Arsenic, All Generated in the Universe: Elucidating Their Environmental Impact Risk on Human Health Including Clinical Liver Injury. *International Journal of Molecular Sciences*, **25**, Article No. 6662. https://doi.org/10.3390/ijms25126662

[20] Chen, C.S., Yuan, T., Lu, T., Lee, H., Chen, Y., Lai, L., *et al*. (2024) Exposure-Associated DNA Methylation among People Exposed to Multiple Industrial Pollutants. *Clinical Epigenetics*, **16**, Article No. 111. https://doi.org/10.1186/s13148-024-01705-y

[21] Tam, L.M., Price, N.E. and Wang, Y. (2020) Molecular Mechanisms of Arsenic-Induced Disruption of DNA Repair. *Chemical Research in Toxicology*, **33**, 709-726. https://doi.org/10.1021/acs.chemrestox.9b00464

[22] Zhao, L.J., *et al*. (2023) DNA Methylation and Expression Changes of Ferroptosis Related Genes SLC7A11 and CDKN1A in Human Hepatic Stellate Cell Activation Induced by Sodium Arsenite. *Journal of Environmental and Occupational Medicine*, **40**, 1403-1410.

[23] Stößer, S., Lumpp, T., Fischer, F., Gunesch, S., Schumacher, P. and Hartwig, A. (2023) Effect of Long-Term Low-Dose Arsenic Exposure on DNA Methylation and Gene Expression in Human Liver Cells. *International Journal of Molecular Sciences*, **24**, Article No. 15238. https://doi.org/10.3390/ijms242015238

[24] Colwell, M.L., Flack, N., Rezabek, A. and Faulk, C. (2023) Intergenerational Arsenic Exposure on the Mouse Epigenome and Metabolic Physiology. *Environmental and Molecular Mutagenesis*, **64**, 72-87. https://doi.org/10.1002/em.22526

[25] Singh, R.D., Tiwari, R., Sharma, V., Khan, H., Gangopadhyay, S., Singh, S., *et al*. (2023) Prenatal Arsenic Exposure Induces Immunometabolic Alteration and Renal Injury in Rats. *Frontiers in Medicine*, **9**, Article ID: 1045692. https://doi.org/10.3389/fmed.2022.1045692

[26] Hsueh, Y., Chen, M., Lin, Y., Wu, C., Shiue, H., Hsu, S., *et al*. (2024) Associations among Global Long Interspersed Nuclear Element-1 DNA Methylation, Metal Exposure, and Chronic Kidney Disease. *Archives of Toxicology*, **98**, 3127-3135. https://doi.org/10.1007/s00204-024-03780-9

[27] Iheanacho, M.S., Kandel, R., Roy, P. and Singh, K.P. (2023) Epigallocatechin-3-Gallate Attenuates Arsenic-Induced Fibrogenic Changes in Human Kidney Epithelial Cells through Reversal of Epigenetic Aberrations and Antioxidant Activities. *BioFactors*, **50**, 542-557. https://doi.org/10.1002/biof.2027

[28] Yan, M., Wang, H., Wei, R. and Li, W. (2023) Arsenic Trioxide: Applications, Mechanisms of Action, Toxicity and Rescue Strategies to Date. *Archives of Pharmacal Research*, **47**, 249-271. https://doi.org/10.1007/s12272-023-01481-y

[29] Lumour-Mensah, T. and Lemos, B. (2024) Defining High Confidence Targets of Differential Cpg Methylation in Response to in Utero Arsenic Exposure and Implications for Cancer Risk. *Toxicology and Applied Pharmacology*, **482**, Article ID: 116768.

https://doi.org/10.1016/j.taap.2023.116768

[30] Wang, C., Wang, B., Wei, Y., Li, S., Ren, J., Dai, Y., *et al*. (2024) Effect of *Gentianella acuta* (michx.) Hulten against the Arsenic-Induced Development Hindrance of Mouse Oocytes. *BioMetals*, **37**, 1411-1430. https://doi.org/10.1007/s10534-024-00613-1

[31] Lerma-Treviño, C., Hernández-Cadena, L., Acosta-Montes, J.O., Hernández-Montes, G., Alvarado-Cruz, I., Romieu, I., *et al*. (2024) Prenatal Arsenic Exposure on DNA Methylation of C18ORF8 and ADAMTS9 Genes of Newborns from the POSGRAD Birth Cohort Study. *Toxics*, **12**, Article No. 476. https://doi.org/10.3390/toxics12070476

[32] Liu, J., Gunewardena, S., Yue Cui, J., Klaassen, C.D., Chorley, B.N. and Corton, J.C. (2020) Transplacental Arsenic Exposure Produced 5-Methylcytosine Methylation Changes and Aberrant microRNA Expressions in Livers of Male Fetal Mice. *Toxicology*, **435**, Article ID: 152409. https://doi.org/10.1016/j.tox.2020.152409

[33] Lumour-Mensah, T. and Lemos, B. (2024) Evidence of Reduced Gestational Age in Response to in Utero Arsenic Exposure and Implications for Aging Trajectories of the Newborn. *Environment International*, **185**, Article ID: 108566. https://doi.org/10.1016/j.envint.2024.108566

[34] Gliga, A.R., Engström, K., Kippler, M., Skröder, H., Ahmed, S., Vahter, M., *et al*. (2018) Prenatal Arsenic Exposure Is Associated with Increased Plasma IGFBP3 Concentrations in 9-Year-Old Children Partly via Changes in DNA Methylation. *Archives of Toxicology*, **92**, 2487-2500. https://doi.org/10.1007/s00204-018-2239-3

[35] Dye, C.K., Domingo-Relloso, A., Kupsco, A., Tinkelman, N.E., Spratlen, M.J., Bozack, A.K., *et al*. (2023) Maternal DNA Methylation Signatures of Arsenic Exposure Is Associated with Adult Offspring Insulin Resistance in the Strong Heart Study. *Environment International*, **173**, Article ID: 107774. https://doi.org/10.1016/j.envint.2023.107774

[36] Li, N., Liu, H. and Liu, S. (2024) Deciphering DNA Methylation in Gestational Diabetes Mellitus: Epigenetic Regulation and Potential Clinical Applications. *International Journal of Molecular Sciences*, **25**, Article No. 9361. https://doi.org/10.3390/ijms25179361

[37] Yin, G., Xia, L., Hou, Y., Li, Y., Cao, D., Liu, Y., *et al*. (2021) Transgenerational Male Reproductive Effect of Prenatal Arsenic Exposure: Abnormal Spermatogenesis with Igf2/h19 Epigenetic Alteration in CD1 Mouse. *International Journal of Environmental Health Research*, **32**, 1248-1260. https://doi.org/10.1080/09603123.2020.1870668

[38] Elkin, E.R., Higgins, C., Aung, M.T. and Bakulski, K.M. (2022) Metals Exposures and DNA Methylation: Current Evidence and Future Directions. *Current Environmental Health Reports*, **9**, 673-696. https://doi.org/10.1007/s40572-022-00382-4

[39] Nohara, K., Suzuki, T., Okamura, K., Kawai, T. and Nakabayashi, K. (2025) Acquired Sperm Hypomethylation by Gestational Arsenic Exposure Is Re-Established in both the Paternal and Maternal Genomes of Post-Epigenetic Reprogramming Embryos. *Epigenetics & Chromatin*, **18**, 1-14. https://doi.org/10.1186/s13072-025-00569-7

[40] Wu, L., Li, H., Ye, F., Wei, Y., Li, W., Xu, Y., *et al*. (2022) As3MT-Mediated SAM Consumption, Which Inhibits the Methylation of Histones and LINE1, Is Involved in Arsenic-Induced Male Reproductive Damage. *Environmental Pollution*, **313**, Article ID: 120090. https://doi.org/10.1016/j.envpol.2022.120090

[41] Wang, Z., Wang, P. and Yang, C. (2024) Dysregulation of Long Non-Coding RNAs—The Novel Lnc in Metal Toxicity and Carcinogenesis. *Current Environmental Health Reports*, **12**, Article No. 3. https://doi.org/10.1007/s40572-024-00468-1

[42] Hsueh, Y., Chen, W., Lee, H., Huang, Y., Shiue, H., Hsu, S., *et al*. (2023) Global DNA Methylation and the Association between Metal Exposure and Chronic Kidney Disease. *Frontiers in Public Health*, **11**, Article ID: 1104692. https://doi.org/10.3389/fpubh.2023.1104692

[43] Zhou, Q. and Xi, S. (2018) A Review on Arsenic Carcinogenesis: Epidemiology, Metabolism, Genotoxicity and Epigenetic Changes. *Regulatory Toxicology and Pharmacology*, **99**, 78-88. https://doi.org/10.1016/j.yrtph.2018.09.010

[44] Wei, S., Wang, W., Liu, S., Sun, B., Zeng, Q., Wang, G., *et al*. (2022) Genome-Wide DNA Methylation Pattern in Whole Blood of Patients with Coal-Burning Arsenic Poisoning. *Ecotoxicology and Environmental Safety*, **248**, Article ID: 114323. https://doi.org/10.1016/j.ecoenv.2022.114323

[45] Jiménez-Garza, O., Ghosh, M., Barrow, T.M. and Godderis, L. (2023) Toxicomethylomics Revisited: A State-of-the-Science Review about DNA Methylation Modifications in Blood Cells from Workers Exposed to Toxic Agents. *Frontiers in Public Health*, **11**, Article ID: 1073658. https://doi.org/10.3389/fpubh.2023.1073658

[46] Ghosh, S., Chakraborty, A., Das, N., Bhowmick, S., Majumdar, K.K., Bhattacharjee, S., *et al*. (2025) AS3MT Gene Variant Shows Association with Skin Lesions in an Arsenic Exposed Population of India. *Biological Trace Element Research*, **203**, 4516-4528. https://doi.org/10.1007/s12011-025-04515-2

[47] Yu, G., Wu, L., Su, Q., Ji, X., Zhou, J., Wu, S., *et al*. (2024) Neurotoxic Effects of Heavy Metal Pollutants in the Environment: Focusing on Epigenetic Mechanisms. *Environmental Pollution*, **345**, Article ID: 123563. https://doi.org/10.1016/j.envpol.2024.123563

[48] Wei, Y., Zhou, Y., Xiao, L., Qin, J., Cheng, H., Cai, H., *et al*. (2024) Associations of Heavy Metals with Cognitive Function: An Epigenome-wide View of DNA Methylation and Mediation Analysis. *Annals of Neurology*, **96**, 87-98. https://doi.org/10.1002/ana.26942

[49] Schmidt, S. (2024) Marking Time: Epigenetic Aging May Partially Explain the Arsenic-Cardiovascular Disease Link. *Environmental Health Perspectives*, **132**, Article No. 24001. https://doi.org/10.1289/ehp14287

[50] Karachaliou, C., Sgourou, A., Kakkos, S. and Kalavrouziotis, I. (2021) Arsenic Exposure Promotes the Emergence of Cardiovascular Diseases. *Reviews on Environmental Health*, **37**, 467-486. https://doi.org/10.1515/reveh-2021-0004

[51] Sevak, P. and Pushkar, B. (2024) Arsenic Pollution Cycle, Toxicity and Sustainable Remediation Technologies: A Comprehensive Review and Bibliometric Analysis. *Journal of Environmental Management*, **349**, Article ID: 119504. https://doi.org/10.1016/j.jenvman.2023.119504

[52] Golui, D., Raza, M.B., Roy, A., Mandal, J., Sahu, A.K., Ray, P., *et al*. (2023) Arsenic in the Soil-Plant-Human Continuum in Regions of Asia: Exposure and Risk Assessment. *Current Pollution Reports*, **9**, 760-783. https://doi.org/10.1007/s40726-023-00279-2

[53] Yamamoto, T., Gi, M., Yamashita, S., Suzuki, S., Fujioka, M., Vachiraarunwong, A., *et al*. (2023) DNA Methylation Aberrations in Dimethylarsinic Acid-Induced Bladder Carcinogenesis. *Cancers*, **15**, Article No. 5274. https://doi.org/10.3390/cancers15215274

[54] Porten, S.P. (2018) Epigenetic Alterations in Bladder Cancer. *Current Urology Reports*, **19**, Article No. 102. https://doi.org/10.1007/s11934-018-0861-5

[55] Chung, F.F., Khoueiry, R., Sallé, A., Cuenin, C., Bošković, M. and Herceg, Z. (2024)

Sodium Arsenite-Induced DNA Methylation Alterations Exacerbated by P53 Knockout in MCF7 Cells. *Heliyon*, **10**, e39548. https://doi.org/10.1016/j.heliyon.2024.e39548

[56] Wang, P., Liu, Z., Sweef, O., Xie, J., Chen, J., Zhu, H., *et al.* (2024) Long Noncoding RNA ABHD11-AS1 Interacts with SART3 and Regulates CD44 RNA Alternative Splicing to Promote Lung Carcinogenesis. *Environment International*, **185**, Article ID: 108494. https://doi.org/10.1016/j.envint.2024.108494

[57] Gao, Y., Takenaka, K., Xu, S., Cheng, Y. and Janitz, M. (2025) Recent Advances in Investigation of circR-NA/lncRNA-miRNA-mRNA Networks through RNA Sequencing Data Analysis. *Briefings in Functional Genomics*, **24**, elaf005. https://doi.org/10.1093/bfgp/elaf005

[58] Sayed, N.H., Hammad, M., Abdelrahman, S.A. and Abdelgawad, H.M. (2024) Association of Long Non-Coding RNAs and ABO Blood Groups with Acute Lymphoblastic Leukemia in Egyptian Children. *Non-Coding RNA Research*, **9**, 307-317. https://doi.org/10.1016/j.ncrna.2024.01.010

[59] Gaál, Z. (2024) Role of microRNAs in Immune Regulation with Translational and Clinical Applications. *International Journal of Molecular Sciences*, **25**, Article No. 1942. https://doi.org/10.3390/ijms25031942

[60] Lv, Y., Wang, H., Zheng, D., Shi, M., Bi, D., Hu, Q., *et al.* (2024) Environmental Arsenic Pollution Induced Liver Oxidative Stress Injury by Regulating miR-155 through Inhibition of AUF1. *Science of the Total Environment*, **922**, Article ID: 171237. https://doi.org/10.1016/j.scitotenv.2024.171237

[61] Barangi, S., Mehri, S., Moosavi, Z., Yarmohammadi, F., Hayes, A.W. and Karimi, G. (2024) Melatonin Attenuates Liver Injury in Arsenic-Treated Rats: The Potential Role of the Nrf2/HO-1, Apoptosis, and miR-34a/Sirt1/Autophagy Pathways. *Journal of Biochemical and Molecular Toxicology*, **38**, e23635. https://doi.org/10.1002/jbt.23635

[62] Sun, J., Wu, L., Wu, M., Liu, Q. and Cao, H. (2023) Non-Coding RNA Therapeutics: Towards a New Candidate for Arsenic-Induced Liver Disease. *Chemico-Biological Interactions*, **382**, Article ID: 110626. https://doi.org/10.1016/j.cbi.2023.110626

[63] Xue, J., Xiao, T., Wei, S., Sun, J., Zou, Z., Shi, M., *et al.* (2021) miR-21-Regulated M2 Polarization of Macrophage Is Involved in Arsenicosis-Induced Hepatic Fibrosis through the Activation of Hepatic Stellate Cells. *Journal of Cellular Physiology*, **236**, 6025-6041. https://doi.org/10.1002/jcp.30288

[64] Li, W., Wu, L., Sun, Q., Yang, Q., Xue, J., Shi, M., *et al.* (2021) MicroRNA-191 Blocking the Translocation of GLUT4 Is Involved in Arsenite-Induced Hepatic Insulin Resistance through Inhibiting the IRS1/AKT Pathway. *Ecotoxicology and Environmental Safety*, **215**, Article ID: 112130. https://doi.org/10.1016/j.ecoenv.2021.112130

[65] Cai, X., Yu, L., Chen, Z., Ye, F., Ren, Z. and Jin, P. (2020) Arsenic Trioxide-Induced Upregulation of Mir-1294 Suppresses Tumor Growth in Hepatocellular Carcinoma by Targeting TEAD1 and Pim1. *Cancer Biomarkers*, **28**, 221-230. https://doi.org/10.3233/cbm-190490

[66] Zhang, M., Li, L. and Li, S. (2024) The Role of miR-150-5p/SOCS1 Pathway in Arsenic-Induced Pyroptosis of LX-2 Cells. *Biological Trace Element Research*, **203**, 822-834. https://doi.org/10.1007/s12011-024-04211-7

[67] Dong, Q., Fu, H. and Jiang, H. (2024) The Role of Exosome-Shuttled miRNAs in Heavy Metal-Induced Peripheral Tissues and Neuroinflammation in Alzheimer's Disease. *Biomedicine & Pharmacotherapy*, **176**, Article ID: 116880. https://doi.org/10.1016/j.biopha.2024.116880

[68] Abdel-Wahab, B.A., El-Shoura, E.A.M., Shafiuddin Habeeb, M. and Zafaar, D. (2023)

Febuxostat Alleviates Arsenic Trioxide-Induced Renal Injury in Rats: Insights on the Crosstalk between NLRP3/TLR4, Sirt-1/NF-κB/TGF-β Signaling Pathways, and miR-23b-3p, miR-181a-5b Expression. *Biochemical Pharmacology*, **216**, Article ID: 115794. https://doi.org/10.1016/j.bcp.2023.115794

[69] Ghafouri-Fard, S., Shoorei, H., Dabiri Oskuei, S., Hussen, B.M., Rasool Abdullah, S., Taheri, M., *et al*. (2023) The Interaction between miRNAs and Hazardous Materials. *Non-Coding RNA Research*, **8**, 507-519. https://doi.org/10.1016/j.ncrna.2023.06.005

[70] Ganie, S.Y., Javaid, D., Hajam, Y.A. and Reshi, M.S. (2023) Arsenic Toxicity: Sources, Pathophysiology and Mechanism. *Toxicology Research*, **13**, tfad111. https://doi.org/10.1093/toxres/tfad111

[71] Zhang, X., Jackson, S., Liu, J., Li, J., Yang, Z., Sun, D., *et al*. (2024) Arsenic Aggravates the Progression of Diabetic Nephropathy through miRNA-mRNA-Autophagy Axis. *Food and Chemical Toxicology*, **187**, Article ID: 114628. https://doi.org/10.1016/j.fct.2024.114628

[72] Chittilla, M., Uzoma, C., Brewer, D. and Razzaque, M.S. (2024) Potential Association between Arsenic and Vitamin D. *Frontiers in Endocrinology*, **15**, Article ID: 1430980. https://doi.org/10.3389/fendo.2024.1430980

[73] Shakya, A., Dodson, M., Artiola, J.F., Ramirez-Andreotta, M., Root, R.A., Ding, X., *et al*. (2023) Arsenic in Drinking Water and Diabetes. *Water*, **15**, Article No. 1751. https://doi.org/10.3390/w15091751

[74] Liu, Q. and Lei, Z. (2023) The Role of microRNAs in Arsenic-Induced Human Diseases: A Review. *Journal of Agricultural and Food Chemistry*, **71**, 16855-16882. https://doi.org/10.1021/acs.jafc.3c03721

[75] Chen, X., Wu, R., Wu, H., Hu, Y., Wang, H., Fu, J., *et al*. (2023) Integrated miRNA-mRNA Analysis Reveals the Dysregulation of Lipid Metabolism in Mouse Liver Induced by Developmental Arsenic Exposure. *Journal of Hazardous Materials*, **445**, Article ID: 130459. https://doi.org/10.1016/j.jhazmat.2022.130459

[76] Howe, C.G., Armstrong, D.A., Muse, M.E., Gilbert-Diamond, D., Gui, J., Hoen, A.G., *et al*. (2022) Periconceptional and Prenatal Exposure to Metals and Extracellular Vesicle and Particle miRNAs in Human Milk: A Pilot Study. *Exposure and Health*, **15**, 731-743. https://doi.org/10.1007/s12403-022-00520-1

[77] Mukherjee, A.G. and Gopalakrishnan, A.V. (2024) Arsenic-induced Prostate Cancer: An Enigma. *Medical Oncology*, **41**, Article No. 50. https://doi.org/10.1007/s12032-023-02266-5

[78] Ji, H., Bi, Z., Pawar, A.S., Seno, A., Almutairy, B.S., Fu, Y., *et al*. (2024) Genomic and Epigenetic Characterization of the Arsenic-Induced Oncogenic microRNA-21. *Environmental Pollution*, **345**, Article ID: 123396. https://doi.org/10.1016/j.envpol.2024.123396

[79] Xu, T., Xie, M., Jing, X., Cui, J., Wu, X. and Shu, Y. (2021) Crosstalk between Environmental Inflammatory Stimuli and Non-Coding RNA in Cancer Occurrence and Development. *Cancers*, **13**, Article No. 4436. https://doi.org/10.3390/cancers13174436

[80] Li, Y., Zhao, Q., Yao, J., Lv, C., Gao, Y., Sun, D., *et al*. (2023) MiR-96-5p Suppresses Progression of Arsenite-Induced Human Keratinocyte Proliferation and Malignant Transformation by Targeting Denticleless E3 Ubiquitin Protein Ligase Homolog. *Toxics*, **11**, Article No. 978. https://doi.org/10.3390/toxics11120978

[81] Aalami, A.H., Hoseinzadeh, M., Hosseini Manesh, P., Jiryai Sharahi, A. and Kargar Aliabadi, E. (2022) Carcinogenic Effects of Heavy Metals by Inducing Dysregulation

of microRNAs: A Review. *Molecular Biology Reports*, **49**, 12227-12238. https://doi.org/10.1007/s11033-022-07897-x

[82] Nguyen, H.D. and Kim, M. (2022) Exposure to a Mixture of Heavy Metals Induces Cognitive Impairment: Genes and microRNAs Involved. *Toxicology*, **471**, Article ID: 153164. https://doi.org/10.1016/j.tox.2022.153164

[83] Lei, W., Zhang, L., Chen, J., Zheng, G., Guo, L., Jiang, T., *et al*. (2024) The Role and Mechanism of miR-425-3p Regulating Neuronal Pyroptosis-Mediated Inorganic Arsenic-Induced Generalized Anxiety Disorder. *Ecotoxicology and Environmental Safety*, **269**, Article ID: 115781. https://doi.org/10.1016/j.ecoenv.2023.115781

[84] Mishra, S., Kalra, N., Botlagunta, M. and Rajasekaran, S. (2024) MicroRNA-195-5p Mediates Arsenic-Induced Cytotoxicity in Human Lung Epithelial Cells: Beneficial Role of Plant-Derived Tannic Acid. *Toxicology and Applied Pharmacology*, **482**, Article ID: 116775. https://doi.org/10.1016/j.taap.2023.116775

[85] Chen, Y., Cheng, C. and Chen, L. (2024) Multifaceted Role of microRNA-301a in Human Cancer: From Biomarker Potential to Therapeutic Targeting. *Cancer Gene Therapy*, **31**, 1754-1764. https://doi.org/10.1038/s41417-024-00832-1

[86] Islam, R., Zhao, L., Zhang, X. and Liu, L. (2023) MiR-218-5p/EGFR Signaling in Arsenic-Induced Carcinogenesis. *Cancers*, **15**, Article No. 1204. https://doi.org/10.3390/cancers15041204

[87] Wang, P., Xiao, T., Li, J., Wang, D., Sun, J., Cheng, C., *et al*. (2021) miR-21 in EVs from Pulmonary Epithelial Cells Promotes Myofibroblast Differentiation via Glycolysis in Arsenic-Induced Pulmonary Fibrosis. *Environmental Pollution*, **286**, Article ID: 117259. https://doi.org/10.1016/j.envpol.2021.117259

[88] Shen, X., Zhi, F., Shi, C., Xu, J., Chao, Y., Xu, J., *et al*. (2023) Correction: The Involvement and Therapeutic Potential of lncRNA Kcnq1ot1/miR-34a-5p/Sirt1 Pathway in Arsenic Trioxide-Induced Cardiotoxicity. *Journal of Translational Medicine*, **21**, Article No. 52. https://doi.org/10.1186/s12967-023-03982-2

[89] Mahadik, S.R., Reddy, A.R.T., Choudhary, K., Nama, L., Jamdade, M.S., Singh, S., *et al*. (2024) Arsenic Induced Cardiotoxicity: An Approach for Molecular Markers, Epigenetic Predictors and Targets. *Environmental Toxicology and Pharmacology*, **111**, Article ID: 104558. https://doi.org/10.1016/j.etap.2024.104558

[90] Todero, J.E., Koch-Laskowski, K., Shi, Q., Kanke, M., Hung, Y., Beck, R., *et al*. (2022) Candidate Master microRNA Regulator of Arsenic-Induced Pancreatic Beta Cell Impairment Revealed by Multi-Omics Analysis. *Archives of Toxicology*, **96**, 1685-1699. https://doi.org/10.1007/s00204-022-03263-9

[91] Sira, J., Zhang, X., Gao, L., Wabo, T.M.C., Li, J., Akiti, C., *et al*. (2023) Effects of Inorganic Arsenic on Type 2 Diabetes Mellitus *in Vivo*: The Roles and Mechanisms of miRNAs. *Biological Trace Element Research*, **202**, 111-121. https://doi.org/10.1007/s12011-023-03669-1

[92] Nail, A.N., Xu, M., Bastick, J.C., Patel, D.P., Rogers, M.N. and States, J.C. (2023) Arsenic and Human Health: New Molecular Mechanisms for Arsenic-Induced Cancers. *Current Pollution Reports*, **9**, 784-797. https://doi.org/10.1007/s40726-023-00278-3

[93] Li, P., Ge, H., Zhao, J., Zhou, Y., Zhou, J., Li, P., *et al*. (2023) Disrupting of IGF2BP3-Stabilized HK2 mRNA by MYO16-AS1 Competitively Binding Impairs LUAD Migration and Invasion. *Molecular and Cellular Biochemistry*, **479**, 2795-2808. https://doi.org/10.1007/s11010-023-04887-w

[94] Xiang, S., Yan, W., Ren, X., Feng, J. and Zu, X. (2024) Role of Ferroptosis and Ferroptosis-Related Long Non'coding RNA in Breast Cancer. *Cellular & Molecular Biology Letters*, **29**, Article No. 40. https://doi.org/10.1186/s11658-024-00560-2

[95] Ferro, A., Saccu, G., Mattivi, S., Gaido, A., Herrera Sanchez, M.B., Haque, S., *et al*. (2024) Extracellular Vesicles as Delivery Vehicles for Non-Coding RNAs: Potential Biomarkers for Chronic Liver Diseases. *Biomolecules*, **14**, Article No. 277. https://doi.org/10.3390/biom14030277

[96] Islam, R., Zhao, L., Wang, Y., Lu-Yao, G. and Liu, L. (2022) Epigenetic Dysregulations in Arsenic-Induced Carcinogenesis. *Cancers*, **14**, Article No. 4502. https://doi.org/10.3390/cancers14184502

[97] Dai, X., Chen, C., Xue, J., Xiao, T., Mostofa, G., Wang, D., *et al*. (2019) Exosomal MALAT1 Derived from Hepatic Cells Is Involved in the Activation of Hepatic Stellate Cells via miRNA-26b in Fibrosis Induced by Arsenite. *Toxicology Letters*, **316**, 73-84. https://doi.org/10.1016/j.toxlet.2019.09.008

[98] Wu, M., Sun, J., Wang, L., Wang, P., Xiao, T., Wang, S., *et al*. (2023) The lncRNA HOTAIR via miR-17-5p Is Involved in Arsenite-Induced Hepatic Fibrosis through Regulation of Th17 Cell Differentiation. *Journal of Hazardous Materials*, **443**, Article ID: 130276. https://doi.org/10.1016/j.jhazmat.2022.130276

[99] Dong, Z., Gao, M., Li, C., Xu, M. and Liu, S. (2020) LncRNA UCA1 Antagonizes Arsenic-Induced Cell Cycle Arrest through Destabilizing EZH2 and Facilitating NFATc2 Expression. *Advanced Science*, **7**, Article ID: 1903630. https://doi.org/10.1002/advs.201903630

[100] Zhang, Z., Shi, S., Li, J. and Costa, M. (2023) Long Non-Coding RNA MEG3 in Metal Carcinogenesis. *Toxics*, **11**, Article No. 157. https://doi.org/10.3390/toxics11020157

[101] Tan, J., Sun, M., Luo, Q., Sun, H., Wang, M., Jiang, C., *et al*. (2020) Arsenic Exposure Increased Expression of HOTAIR and LincRNA-p21 *in Vivo* and *Vitro*. *Environmental Science and Pollution Research*, **28**, 587-596. https://doi.org/10.1007/s11356-020-10487-8

[102] Adeogun, A.E., Ogunleye, O.D., Akhigbe, T.M., Oyedokun, P.A., Adegbola, C.A., Saka, W.A., *et al*. (2024) Impact of Arsenic on Male and Female Reproductive Function: A Review of the Pathophysiology and Potential Therapeutic Strategies. *Naunyn-Schmiedeberg's Archives of Pharmacology*, **398**, 1283-1297. https://doi.org/10.1007/s00210-024-03452-6

[103] Bu, N., Song, H.Y. and Wang, S.H. (2022) Research Progress on the Regulatory Mechanism of Non-Coding RNA in Arsenic Toxicity. *Chinese Journal of Industrial Hygiene and Occupational Diseases*, **40**, 316-320.

[104] Chu, F., Lu, C., Jiao, Z., Yang, W., Yang, X., Ma, H., *et al*. (2023) Unveiling the LncRNA-miRNA-mRNA Regulatory Network in Arsenic-Induced Nerve Injury in Rats through High-Throughput Sequencing. *Toxics*, **11**, Article No. 953. https://doi.org/10.3390/toxics11120953

[105] Xiao, T., Zou, Z., Xue, J., Syed, B.M., Sun, J., Dai, X., *et al*. (2021) LncRNA H19-Mediated M2 Polarization of Macrophages Promotes Myofibroblast Differentiation in Pulmonary Fibrosis Induced by Arsenic Exposure. *Environmental Pollution*, **268**, Article ID: 115810. https://doi.org/10.1016/j.envpol.2020.115810

[106] Wang, M., Tan, J., Jiang, C., Li, S., Wu, X., Ni, G., *et al*. (2020) Inorganic Arsenic Influences Cell Apoptosis by Regulating the Expression of MEG3 Gene. *Environmental Geochemistry and Health*, **43**, 475-484. https://doi.org/10.1007/s10653-020-00740-x

[107] Yu, J., Li, S., Shen, S., Zhou, Q., Yin, J., Zhao, R., *et al*. (2023) The Transcript NR 134251.1 of lncRNA APTR with an Opposite Function to All Transcripts Inhibits Proliferation and Induces Apoptosis by Regulating Proliferation and Apoptosis-Related Genes. *Human & Experimental Toxicology*, **42**.

https://doi.org/10.1177/09603271221150247

[108] Chen, Q., Sun, M., Cheng, H., Qi, J., Tan, J., Gu, Y., *et al*. (2023) Inorganic Arsenic-Mediated Upregulation of TUG1 Promotes Apoptosis in Human Bronchial Epithelial Cells by Activating the P53 Signaling Pathway. *Toxicology and Industrial Health*, **39**, 700-711. https://doi.org/10.1177/07482337231209349

[109] Ghafouri-Fard, S., Pourtavakoli, A., Hussen, B.M., Taheri, M. and Kiani, A. (2023) A Review on the Importance of LINC-ROR in Human Disorders. *Pathology—Research and Practice*, **244**, Article ID: 154420. https://doi.org/10.1016/j.prp.2023.154420

[110] Pan, X., Li, C. and Feng, J. (2023) The Role of LncRNAs in Tumor Immunotherapy. *Cancer Cell International*, **23**, Article No. 30. https://doi.org/10.1186/s12935-023-02872-3

[111] Bernasconi, R. and Kuster, G.M. (2024) Non-Coding RNAs and Their Potential Exploitation in Cancer Therapy-related Cardiotoxicity. *British Journal of Pharmacology*, **182**, 296-315. https://doi.org/10.1111/bph.16416

[112] Jiang, Y., Shen, X., Zhi, F., Wen, Z., Gao, Y., Xu, J., *et al*. (2023) An Overview of Arsenic Trioxide-Involved Combined Treatment Algorithms for Leukemia: Basic Concepts and Clinical Implications. *Cell Death Discovery*, **9**, Article No. 266. https://doi.org/10.1038/s41420-023-01558-z

[113] Jiang, C., Sun, M., Li, S., Tan, J., Wang, M. and He, Y. (2021) Long Non-Coding RNA DICER1-AS1-Low Expression in Arsenic-Treated A549 Cells Inhibits Cell Proliferation by Regulating the Cell Cycle Pathway. *Environmental Toxicology and Pharmacology*, **84**, Article ID: 103617. https://doi.org/10.1016/j.etap.2021.103617

[114] Wang, Y., Yang, T., Han, Y., Ren, Z., Zou, J., Liu, J., *et al*. (2020) lncRNA OTUD6B-AS1 Exacerbates As(2)O(3)-Induced Oxidative Damage in Bladder Cancer via Mir-6734-5p-Mediated Functional Inhibition of IDH2. *Oxidative Medicine and Cellular Longevity*, **2020**, Article ID: 3035624. https://doi.org/10.1155/2020/3035624

[115] Zhou, W., Wang, M., Wang, L., Liu, Y., Tian, Z., Xie, L., *et al*. (2025) Epigenetics in Plant Response to Climate Change. *Biology*, **14**, Article No. 631. https://doi.org/10.3390/biology14060631

[116] Zhang, J. and Zhao, F. (2025) Circular RNA Discovery with Emerging Sequencing and Deep Learning Technologies. *Nature Genetics*, **57**, 1089-1102. https://doi.org/10.1038/s41588-025-02157-7

[117] Hashemi, M., Daneii, P., Asadalizadeh, M., Tabari, K., Matinahmadi, A., Bidoki, S.S., *et al*. (2024) Epigenetic Regulation of Hepatocellular Carcinoma Progression: MicroRNAs as Therapeutic, Diagnostic and Prognostic Factors. *The International Journal of Biochemistry & Cell Biology*, **170**, Article ID: 106566. https://doi.org/10.1016/j.biocel.2024.106566

[118] Gomez, E.W., De Paula, L.B., Weimer, R.D., Hellwig, A.H.d.S., Rodrigues, G.M., Alegretti, A.P., *et al*. (2024) The Potential of circHIPK3 as a Biomarker in Chronic Myeloid Leukemia. *Frontiers in Oncology*, **14**, Article ID: 1330592. https://doi.org/10.3389/fonc.2024.1330592

[119] Dawoud, A., Elmasri, R.A., Mohamed, A.H., Mahmoud, A., Rostom, M.M. and Youness, R.A. (2024) Involvement of circRNAs in Regulating the "New Generation of Cancer Hallmarks": A Special Depiction on Hepatocellular Carcinoma. *Critical Reviews in Oncology/Hematology*, **196**, Article ID: 104312. https://doi.org/10.1016/j.critrevonc.2024.104312

[120] Zhang, H., Pei, S., Li, J., Zhu, J., Li, H., Wu, G., *et al*. (2024) Insights about Exosomal Circular RNAs as Novel Biomarkers and Therapeutic Targets for Hepatocellular Carcinoma. *Frontiers in Pharmacology*, **15**, Article ID: 1466424.

https://doi.org/10.3389/fphar.2024.1466424

[121] Huang, Z., Wang, H. and Ji, Z. (2021) CircRNA-100284 Activates Aurora Kinase B by Inducing Methylation of HSP70 via microRNA-217 to Promote Proliferation of Bladder Cancer Cells. *Journal of Cancer Research and Clinical Oncology*, **147**, 703-712. https://doi.org/10.1007/s00432-020-03468-4

[122] Li, D., Li, Z., Yang, Y., Zeng, X., Li, Y., Du, X., *et al*. (2020) Circular RNAs as Biomarkers and Therapeutic Targets in Environmental Chemical Exposure-Related Diseases. *Environmental Research*, **180**, Article ID: 108825. https://doi.org/10.1016/j.envres.2019.108825

[123] Liu, Z., He, Q., Liu, Y., Zhang, Y., Cui, M., Peng, H., *et al*. (2021) Hsa_circ_0005915 Promotes n,n-Dimethylformamide-Induced Oxidative Stress in HL-7702 Cells through NRF2/ARE Axis. *Toxicology*, **458**, Article ID: 152838. https://doi.org/10.1016/j.tox.2021.152838

[124] Mao, Y., Zhou, Q., Wang, J., Zhao, R., Yang, X., Shi, Y., *et al*. (2022) CircP50 Functions through the Phosphorylation- and Acetylation-Activated p53 Pathway to Mediate Inorganic Arsenic-Induced Apoptosis in A549 Cells. *Environmental Science and Pollution Research*, **29**, 91232-91240. https://doi.org/10.1007/s11356-022-22094-w

[125] Li, X., Chen, S., Wang, X., Zhang, R., Yang, J., Xu, H., *et al*. (2022) The Pivotal Regulatory Factor circBRWD1 Inhibits Arsenic Exposure-Induced Lung Cancer Occurrence by Binding mRNA and Regulating Its Stability. *Molecular Therapy—Oncolytics*, **26**, 399-412. https://doi.org/10.1016/j.omto.2022.08.006

[126] Tan, J., Sun, M., Yin, J., Zhou, Q., Zhao, R., Chen, Q., *et al*. (2022) Hsa_circ_0005050 Interacts with ILF3 and Affects Cell Apoptosis and Proliferation by Disrupting the Balance between p53 and p65. *Chemico-Biological Interactions*, **368**, Article ID: 110208. https://doi.org/10.1016/j.cbi.2022.110208

[127] Joghataie, P., Ardakani, M.B., Sabernia, N., Salary, A., Khorram, S., Sohbatzadeh, T., *et al*. (2024) The Role of Circular RNA in the Pathogenesis of Chemotherapy-Induced Cardiotoxicity in Cancer Patients: Focus on the Pathogenesis and Future Perspective. *Cardiovascular Toxicology*, **24**, 1151-1167. https://doi.org/10.1007/s12012-024-09914-w

[128] Cheng, Z., Qin, W., Li, S., Shao, S. and Liu, B. (2023) Emerging Roles of Circular RNAs in Cancer Therapy-Induced Cardiotoxicity. *Frontiers in Cardiovascular Medicine*, **10**, Article ID: 1152436. https://doi.org/10.3389/fcvm.2023.1152436

[129] Jiang, Y., Shen, X., Dong, C., Zhi, F., Gao, Y., Shi, C., *et al*. (2022) The Whole Transcriptome Analysis and the circRNA-lncRNA Network Construction in Arsenic Trioxide-Treated Mice Myocardium. *Biomedicine & Pharmacotherapy*, **151**, Article ID: 113183. https://doi.org/10.1016/j.biopha.2022.113183

[130] Li, S., Jiang, C., Tan, J., Zhou, Q., Yin, J. and He, Y. (2021) Sodium Arsenite-Mediated Upregulation of circDHX34 Promotes Apoptosis in Hormone-Independent Breast Cancer Cells by Regulating Apoptotic Genes. *Environmental Science and Pollution Research*, **29**, 2728-2736. https://doi.org/10.1007/s11356-021-15891-2

[131] Gao, Y., Xu, H., Zhao, Q., Cai, D., Zhou, X., Chen, X., *et al*. (2025) The Key Regulator circPDE3B Promotes Arsenic-Induced Bladder Carcinogenesis by Affecting STAT3 and NF-κB Stability. *Cell Biology and Toxicology*, **41**, Article No. 91. https://doi.org/10.1007/s10565-025-10038-2

[132] Zhao, R., Zhang, W. and Fan, X. (2024) Circular RNAs: Potential Biomarkers and Therapeutic Targets for Autoimmune Diseases. *Heliyon*, **10**, e23694. https://doi.org/10.1016/j.heliyon.2023.e23694

[133] He, J., Liu, W., Ge, X., Wang, G., Desai, V., Wang, S., *et al*. (2019) Arsenic-Induced Metabolic Shift Triggered by the Loss of miR-199a-5p through Sp1-Dependent DNA Methylation. *Toxicology and Applied Pharmacology*, **378**, Article ID: 114606. https://doi.org/10.1016/j.taap.2019.114606

[134] Huang, W., Li, H., Yu, Q., Xiao, W. and Wang, D.O. (2022) LncRNA-Mediated DNA Methylation: An Emerging Mechanism in Cancer and Beyond. *Journal of Experimental & Clinical Cancer Research*, **41**, Article No. 100. https://doi.org/10.1186/s13046-022-02319-z

[135] Jiang, R., Li, Y., Zhang, A., Wang, B., Xu, Y., Xu, W., *et al*. (2014) The Acquisition of Cancer Stem Cell-Like Properties and Neoplastic Transformation of Human Keratinocytes Induced by Arsenite Involves Epigenetic Silencing of Let-7c via Ras/NF-κB. *Toxicology Letters*, **227**, 91-98. https://doi.org/10.1016/j.toxlet.2014.03.020

[136] Desaulniers, D., Vasseur, P., Jacobs, A., Aguila, M.C., Ertych, N. and Jacobs, M.N. (2021) Integration of Epigenetic Mechanisms into Non-Genotoxic Carcinogenicity Hazard Assessment: Focus on DNA Methylation and Histone Modifications. *International Journal of Molecular Sciences*, **22**, Article No. 10969. https://doi.org/10.3390/ijms222010969

[137] He, Y., Zhang, R., Chen, J., Tan, J., Wang, M. and Wu, X. (2019) The Ability of Arsenic Metabolism Affected the Expression of lncRNA PANDAR, DNA Damage, or DNA Methylation in Peripheral Blood Lymphocytes of Laborers. *Human & Experimental Toxicology*, **39**, 605-613. https://doi.org/10.1177/0960327119897101