MicroRNAs and Xenobiotic Toxicity: An Overview

Satheeswaran Balasubramanian, Kanmani Gunasekaran, Saranyadevi Sasidharan, Vignesh Jeyamanickavel Mathan, Ekambaram Perumal

Molecular Toxicology Laboratory, Department of Biotechnology, Bharathiar University, Coimbatore, 641 046, India

ARTICLE INFO

Keywords: Biomarkers Epigenetics Environment Gene regulation Non-coding RNAs Toxicity

ABSTRACT

The advent of new technologies has paved the rise of various chemicals that are being employed in industrial as well as consumer products. This leads to the accumulation of these xenobiotic compounds in the environment where they pose a serious threat to both target and non-target species. miRNAs are one of the key epigenetic mechanisms that have been associated with toxicity by modulating the gene expression post-transcriptionally. Here, we provide a comprehensive view on miRNA biogenesis, their mechanism of action and their possible role in xenobiotic toxicity. Further, we review the recent in vitro and in vivo studies involved in xenobiotic exposure induced miRNA alterations and the mRNA-miRNA interactions. Finally, we address the challenges associated with the miRNAs in toxicological studies.

1. Introduction

Xenobiotics are chemical compounds foreign to the body or ecosystem that are identified persistently in the environment which are accumulated by means of anthropogenic sources. With a stupendous increase in chemicals being synthesized for various sectors, all these compounds end up being dispersed into the environment posing a risk for all forms of life from microbes to animals including humans [1]. Once they enter the biological systems, they affect the homeostasis of the body leading to various adverse effects including the alteration in the genes. These alterations in the genes are both stable and transient. One aspect of gene expressions upon exposure to these xenobiotics is controlled by epigenetic mechanisms [2]. Epigenetics in simple terms involves the regulation of genes without altering the nucleotide sequence [3]. They control the gene expression on both transcriptional and translational levels. This includes non-coding RNAs. miRNAs are short non protein-coding RNAs of ~22 nucleotides in length. They fine-tune the gene expression in response to various external stimuli, including environmental toxicants [4]. Their role in gene regulation was first identified in Caenorhabditis elegans in the early 90’s.
There, the first identified miRNA (LIN 4) negatively regulated the gene which is involved in the post-transcriptional development (LIN14) [5,6]. Soon, they have been identified to play a major role in the post transcriptional regulation of genes finding their ways in health and other aspects [7]. Their interactions with environmental toxicants are being explored due to their rising importance as quoted by Lema and Cunningham [8] “Increasing evidence that the expression of micro-RNAs is affected by several known toxicants as well as oxidative and other forms of cellular stress certainly suggest an important role of microRNAs in toxicology, which could provide a link between environmental influences and gene expression.”

2. miRNA biogenesis and their mechanism of action

Extensive research has been carried out to understand the synthesis and function of miRNAs with other epigenetic mechanism also regulating miRNA biogenesis [9]. miRNAs are transcribed by RNA polymerase II/III, either from the intron regions of the protein-coding genes (intragenic) or independently with their own (intergenic) promoters [10,11]. The canonical pathway is the major pathway through which the majority of miRNAs are processed. After transcription, pri-miRNAs are processed into pre-miRNAs by a microprocessor complex. This complex includes RNA binding protein DGR8 and a ribonuclease III enzyme Drosha, which cleaves the pri-miRNA duplex to form an overhang at 3′ of pre-miRNA of ~70 nt [10]. Once processed, they are exported to the cytoplasm via exportin 5 (XPO5)/RanGTP complex [12,13]. After the export, Dicer, RNase III endonuclease along with TRBP, cleaves the pre-miRNA to form a mature miRNA complex which has a guide strand and a passenger strand [14]. The passenger and guide strands are selected based on various factors, including thermodynamic stability. They both are loaded into argonate proteins where the passenger strand is subsequently degraded [15]. Various canonical pathways have been elucidated. One such pathway is used by mirtrons, miRNAs that are obtained from introns of mRNA during splicing. Others include miRNAs generated from small nuclear RNA precursors. However, recent research suggests that even in the absence of Dicer, some of the miRNAs can be produced via alternative pathways proving the highly complex machinery which is yet to be studied [16].

Studies on miRNA mediated gene regulation are predominantly based on gene silencing via translational repression and mRNA degradation (Fig. 1), miRNA induced gene silencing is performed by miRISC which consists of the argonate protein and the guide strand. They bind to the specific sequence at the 3′ UTR (MRE) of their target mRNA. A full complementarity of miR:MRE leads to mRNA slicing while most of the miR:MREs are partially complementary leading to translational inhibition and mRNA decay [17]. miRNA has also been shown to bind to the 5′ UTR and other coding regions leading to gene silencing [18]. However, various research has shown the ability of miRNA to induce transcription as well as translation ([19] [20]). Further studies are needed to understand and validate the functional interaction.

3. Role of miRNAs in xenobiotic toxicity

Aberrant expression of miRNAs has been shown to play a major role in disease pathology, including cancer. The miRNAs are being studied for their non-invasive uses in prognosis, diagnosis and therapeutics [21,22]. Various compounds induce carcinogenicity and other forms of toxicity upon exposure to biological systems. Numerous in vitro (Table 1) and in vivo (Table 2) studies have been conducted which provide us an overview of miRNA alteration and their target gene regulation in response to xenobiotic exposure. Most of the studies use a variety of techniques to study miRNAs key aspects. This includes miRNAs identification, in silico prediction, expression and functional validation (Fig. 2). These combined studies help us to better understand how miRNAs are regulated during different toxicant exposure. The reviewed chemicals include major toxicants that are grouped on the basis of their characteristic behaviour and their physio-chemical attributes.

3.1. Carcinogens

BaP, a model polyaromatic hydrocarbon is present in coal tar, tobacco products and some foods, in particular smoked foods, which are well-known for their carcinogenicity. Mostly, aromatic hydrocarbon-induced toxicity is mediated by AHR pathway. An early study conducted by Duan et al. [25] on murine bronchial epithelial cells showed that BaP can induce tumorigenesis by inhibiting CDK6, which plays a key role in G1/S transition using miRNAs (miR-320 and miR-494) . However, further studies on human cell lines did not identify any significant change in these miRNAs upon exposure to BaP. This could be due to variable changes, including the fact that the expression of miRNAs and their regulation has been shown to be spatio-temporal. Interestingly, the other studies consistently showed that miRNAs alteration targets cell proliferation and survival pathways upon exposure to BaP [40]. Similarly, some of the miRNAs (miRNA-29b, miRNA-26a-1, and miRNA-122) have been shown to regulate numerous pathways like cell cycle, apoptosis and DNA damage repair concordantly [27].

Dioxins are a group of halogenated aromatic hydrocarbons known to induce various toxicity including cancer. In the mouse model, exposure to dioxin showed alteration in the levels of miR-101a and miR-122. The miR-101a targets the COX2 which catalyses the prostanooid signalling pathway leading to liver damage [66]. Also, miR-122 role in cell proliferation and its alteration upon exposure to xenobiotics has been reported earlier [27]. TCDD in zebrafish embryos disrupted the normal homeostasis development with the deregulation of miRNAs prominently involved in haematopoiesis and cardiovascular development (miR-451, miR-23a, miR-23b, miR-24 and miR-27e). They used a variety of methods to identify the altered miRNAs including microarrays, SOLiD sequencing and qRT-PCR and identified only one miRNA (miR-27e) that was differentially expressed [68]. Bisphenol A is a widely used chemical with endocrine disruption and carcinogenic activity. It alters the miRNA (miR-22) involved in the MAPK pathway by targeting ARRB1, NET1, IL1R1, and HSPA1A in HepG2 cells [16].

An interesting study by Xu et al. (2020) have investigated the miRNA alterations in serum of human subjects who were exposed to increased quantities of PFAS through drinking water. Xu et al. identified that the repression of miR-101−3p, miR-144−3p and miR-19a-3p is in correlation with the target genes that are involved in carcinogenicity, cardiovascular function, and cell proliferation[130]. Circulating miRNAs is being studied recently with the reports of their involvement in various pathologies. This is one of the studies that include the role of exogenous miRNAs in xenobiotic exposure.

3.2. Metals and metalloids

Metals, especially heavy metals, are a major class of environmental contaminants. Research is being conducted to understand the effect of miRNAs in response to metals, including heavy metals, as metals have been known to impair vasculogenesis [101]. Lead, a potent neurotoxicant has been shown to induce BCB leakage in murine choroidal epithelial cells. The mechanistic study showed that the increase in the expression of miR-203 leads to tricellulin mRNA degradation. Tricellulin, a protein in the epithelial cells, helps in the formation of tight junctions in these barriers [36]. Studies on metal-exposed miRNA alterations in pregnant women are scarce. A study by Sanders et al. [72] showed that pregnant women in Mexico had been exposed to heavy metals such as lead and mercury, as evidenced by the presence of lead in the blood (> 5 µg/dL in 10 % of patients) as well as in the patellar and Tibia bones. Increased lead exposure during gestation has been related to premature birth. These patients’ cervical cells were collected to identify miRNAs and their correlation with lead concentration. Two notable miRNAs were identified in the blood (miR-297 and miR-188) which target more than 40 genes and 7 miRNAs were found in the
patellar bone of lead exposed patients. In the same patients, the effect on miRNAs and its negative association with toenail mercury were also reported, which showed the miRNAs alterations (miR-205, miR-125b, let-7b and miR-200c).

Cadmium is a heavy metal exhibiting nephrotoxicity and possibly carcinogenicity. miRNAs have been identified to play a major role in nephrotoxicity. It modulates various miRNAs upon exposure in human kidney cells. Altered miRNAs are involved in oxidative stress mediated apoptotic cell death and most cancer pathways leading to renal proximal tubular toxicity. One of the most deregulated miRNAs (miR-27a-3p) in this study has been previously reported to induce malignancy in lung and liver cell lines [59]. Furthermore, a study on hen spleen identified that miR-33-5q was repressed by cadmium exposure which bears a negative correlation with the AMPK signalling pathway. AMPK
Table 1: In vitro studies with prominently altered miRNAs upon xenobiotic exposure.

| miRNAs     | Cell lines | Toxicant                  | Exposure | Effect                                                                 | Reference                   |
|------------|------------|---------------------------|----------|----------------------------------------------------------------------|-----------------------------|
| miR-200b   | HT-29 and HCT-116 | 5-fluorouracil         | 10 μM for 6 days | Apoptosis induced, cell-cycle arrest, DAMP/haemoagglutinin            | TaqMan miRNA assay [22]     |
| miR-205    | MCF-7 and HepG2  | Nonylphenol           | 12 μM for 2, 4, and 7 days | Apoptosis induced, cell-cycle arrest, MAPK                        | TaqMan miRNA assay [24]     |
| miR-320, miR-494 | Primary murine bronchial epithelial cells | BaP | 0.01 μM, 0.1 μM, and 1 μM for 12, 24, and 48 h | CDK6 inhibited, cell-cycle arrest, G1 phase                         | qRT-PCR [25]                |
| miR-122, miR-143, miR-379 | Primary rat hepatocytes | Trichostatin A | 25 μM for 2, 4, and 7 days | Increased cell proliferation, cell-cycle arrest, G1 phase             | Microarray [26]             |
| miR-29b, miR-26a-1, miR-122 | HepG2 | BaP | 2 μM for 6, 12, 24, and 48 h | BaP-responsive pathway, apoptosis induced, cell-cycle arrest          | Microarray [27]             |
| miR-221    | WRL-68      | MC-LR                   | 10 μg/L for 5, 10, 15, 20, and 25 passages | Cyclin G1 inhibited, tumorigenicity                                   | qRT-PCR and transfection    |
| miR-21     | Hepatocytes | Berberine chloride | 40 μM for 1, 2, 4, and 8 h | Increased mRNA expression, cell-cycle arrest                        | Microarray and qRT-PCR analysis |
| miR-197    | A549        | Octanal                | 0.58 mM for 48 h | Increased phosphorylation of p38 MAPK                                | Microarray and qRT-PCR analysis |
| miR-31, miR-34a, miR-133 | Human Hepatocytes | Rifampicin | 10 μM for 48 h | Alterations in metabolism genes                                      | Microarray and qRT-PCR analysis |
| miR-219, miR-654−3p | Jurkat T cell, Jurkat clone E6−1 | Ag NPs and Ag ions | 0.2 mg/L for 24 h | MT1F and TRIB3 inhibited by miR-219−5p and ENDOGL1 by miR-654−3p | Microarray and qRT-PCR analysis |
| miR-210, miR-221 | LNCaP | MIB and DHT | 100 μM for 24 h | Reduced cell viability, increased apoptosis                           | Microarray sequencing and qRT-PCR analysis |
| miR-222, miR-877 | HepG2 | Vildagliptin | 100 μM for 24 h | Genes involved in cell proliferation and differentiation              | Microarray analysis          |
| miR-541    | GC-1        | MIB                     | 500 μM for 24 h | Cell death                                                             | Microarray analysis          |

(continued on next page)
Table 1 (continued)

| miRNAs             | Cell lines                        | Toxicant                          | Exposure | Effect                          | Analyses                                      | References |
|--------------------|-----------------------------------|------------------------------------|----------|---------------------------------|-----------------------------------------------|------------|
| miR-135            | Mouse-Norval cell line            | MnCl2, 50 μM for 4, 24 and 72 h   |          | Nerve conduction blockage       | qRT-PCR, and miRNA transfection               | [56]       |
| miR-221, miR-92b   | Isogenic fibroblasts              | ZnO, 5 μg/mL for 24 h              |          | Cell cycle arrest and induction of apoptosis | qRT-PCR                                        | [57]       |
| miR-221, miR-92b, miR-96, miR-98, miR-496 | Mouse N2a cells                  | ZnO, 5 μg/mL for 24 h              |          | Cell cycle arrest and induction of apoptosis | qRT-PCR                                        | [58]       |
| miR-494            | Mouse primary brain microvascular endothelial cells | ZnO, 5 μg/mL for 24 h              |          | Cell cycle arrest and induction of apoptosis | qRT-PCR                                        | [59]       |

References:
[45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60], [61], [62]
| Toxicant | Model | miRNA | Target | Effect | Analyses | References |
|----------|-------|-------|--------|--------|----------|------------|
| APAP | Male Crl(SD)IGS rats | miR-298, miR-370 | CYP3A4, CYP2E1 | Induction of hepatic CYP enzymes | Gene expression analysis | [63] |
| CCL4 | Male Crl(SD)IGS rats | miR-298, miR-370 | CYP3A4, CYP2E1 | Induction of hepatic CYP enzymes | Gene expression analysis | [63] |
| RDX | Male Crl(SD)IGS rats | miR-298, miR-370 | CYP3A4, CYP2E1 | Induction of hepatic CYP enzymes | Gene expression analysis | [63] |
| APAP | Female B6C3F1 mice | miR-298, miR-370 | CYP3A4, CYP2E1 | Induction of hepatic CYP enzymes | Gene expression analysis | [63] |
### Table 2 (continued)

| miRNA       | Model                     | Toxicant           | Exposure                                      | Target                         | Effect                                      | Analyses                     | References |
|-------------|---------------------------|--------------------|------------------------------------------------|--------------------------------|--------------------------------------------|------------------------------|------------|
| miR-129-5p, miR-218b, miR-181c | Zebrafish              | Si NPs (62 nm) and PbAc (co-exposure) | Si NPs (3 ng/mL) and PbAc (0.5 mg/mL) for 24 h 600 or 1200 mg/kg for 6 or 24 h post-treatment | STXBPA1, NDFIP2, CELF24 and GSK3b | Calcium homeostasis and ER stress | qRT-PCR and Microarray | [80] |
| miR-122, miR-151a, miR-192, miR-193a, miR-194, miR-21, miR-29c | Male Sprague Dawley rats Migiloglobusabei | Acetaminophen | 0.5, 5, 50, 500 mg/L for 24 and 168 h | P-GP | - | Liver injury | qRT-PCR | [81] |
| miR-27a      |                          |                    |                                                |                                |                                            | qRT-PCR, SOLiD sequencing, qRT-PCR | [82] |
| miR-33-5q    | Hy-Line Brown Chicken    | Cadmium chloride   | 10 mg/kg for 90 days | NF-kB, p-JNK/JNK, p-AKT/ AKT and mTOR | Ion homeostasis disruption | qRT-PCR, RNAi assay | [83] |
| miR-455-3p   | Sprague Dawley Rats      | Cadmium chloride   | 0.6 mg/kg for 12 weeks | miR-27a, miR-455-3p | Genes related to cellular signalling pathways | qRT-PCR, SOLiD sequencing, qRT-PCR | [84] |
| miR-116, miR-77, miR-N10      | Ciliae: Esplioes vannus | AgNPs (73.82 nm) | 15 mg/L for 1 and 12 h | miR-222, miR-486, miR-491 | Increase ROS production, mitochondrial dysfunction | qRT-PCR, SOLiD sequencing, qRT-PCR | [85] |
| miR-204, miR-184 miR-419 | Humans (cokex workers) | 23 urinary metals and ten other urinary OHT-PAs | 0.004-0.3934 μg/L range and 0.1-0.9 μg/L range | SOX9, GSDF, DMR, SMAD4 | Alterations in reproduction process and developmental process | qRT-PCR, SOLiD sequencing, qRT-PCR | [86] |
| miR-125b, miR-125b, miR-155, miR-21 | Silver Carp [C8min] Br | AgNPs (73.82 nm) | 1.095 and 4.380 μg/L for 60 days | miR-503 | - | Oxidative stress and inflammation in the fish spleen | qRT-PCR, RNA-Sequence and bioinformatic analyses | [87] |
| miR-503      | Porcine                  | ZEA                | 0.17 mg/kg, 1.46 mg/kg and 4.58 mg/kg | miR-181a-5p, miR-126-5p | - | - | microRNAs sequencing | [88] |
| miR-184, miR-141 | Sprague Dawley rats | Phthalates          | 20 μg/kg/day; T1: 200 μg/kg/day; T2: 200 μg/kg/day; T3 | miR-16, miR-181, miR-210 | - | Alterations in reproduction, development, metabolism, and rhythmic process | qRT-PCR, RNAi assay | [89] |
| miR-35, miR-38, miR-76, miR-354 | C. elegans | 100 nm nanopoly styrene | 1 μg/L from L1-larvae to adult day-3 | miR-222, miR-486, miR-491 | - | Alterations in reproduction, development, metabolism, and rhythmic process | qRT-PCR, RNAi assay | [90] |
| miR-34a-5p, miR-497-5p, miR-34a-3p, miR-34a-5p | Pigs | Ochratoxin A | 50 μg/kg and 200 μg/kg feed for 28 days | miR-181b-5p, miR-126-5p | - | Alterations in signalling cascades | qRT-PCR, RNAi assay | [91] |
| miR-451a     | Sprague-Dawley rats      | Si NPs             | 1.8 mg/kg b.w, 5.4 mg/kg for 30 days | miR-181b-5p, miR-126-5p, miR-34a-5p | - | - | microRNAs sequencing | [92] |
| miR-367-3p   | C57BL/6 mice             | Melia toosendan sieb et zacc | 10 mg/kg for 6 and 12 h | miR-181b-5p, miR-126-5p, miR-34a-5p | - | - | microRNAs sequencing | [93] |
| miR-181a-5p  | Zebrafish                | Triclosan          | 0, 625, 125 and 250 mg/L | miR-181b-5p, miR-126-5p, miR-34a-5p | - | - | microRNAs sequencing | [94] |
| miR-24, miR-29a, miR-34a, miR-375 | Wistar Albino rats | Zinc oxide NPs | 5 mg/kg for 15 consecutive days | miR-181b-5p, miR-126-5p, miR-34a-5p | - | - | microRNAs sequencing | [95] |
| miR-223, miR-503, miR-10a, miR-200c miR-222 | Mouse lungs | Ricin | 7 μg/kg for 24 h 40 μg/kg for 9 days intraperitoneally | miR-181b-5p, miR-126-5p, miR-34a-5p | - | - | microRNAs sequencing | [96] |
| miR-16, miR-181a-3p, miR-223, miR-451 | Silver Carp | MCLR               | Genes involved in cellular, metabolic and single organism process | miR-181b-5p, miR-126-5p, miR-34a-5p | - | - | Microarray analysis and qRT-PCR | [97] |
| miR-155, miR-338, miR-210 | Humans | Arsenic (form not specified) | 0.5 – 4600 μg/L of arsenic in drinking water | miR-181b-5p, miR-126-5p, miR-34a-5p | - | - | Microarray analysis and qRT-PCR | [98] |
| miR-199a-3, miR-152, miR-7b | Carp fish | Cadmium dichloride hemipentahydrate | 2.5-hexanedione | miR-181b-5p, miR-126-5p, miR-34a-5p | - | - | Microarray analysis and qRT-PCR | [99] |
| miR-181a-5p | Sprague Dawley Rats | Zebrafish          | 0, 3 or 15 mg/kg from gestation day 6 – 19 | miR-181b-5p, miR-126-5p, miR-34a-5p | - | - | Microarray analysis and qRT-PCR | [100] |
in turn, regulates BNIP3−3 dependent autophagy [83]. In rats, the nephrotoxicity induced by cadmium was found to be regulated by miRNA alteration with 44 miRNAs identified to be dysregulated [84]. In one particular study, where carp was exposed to cadmium, around 15 miRNAs were differentially altered which were identified to be players in cell growth and oxidative stress [98].

Copper, another neurotoxicant, has been shown to induce upregulation of miRNAs (miR-200b-3p, miR-200c-3p, miR-205−5p) in human primary microvascular endothelial cells, where the miRNAs target the suppression of LRP1 protein. The latter plays a significant role in brain Aβ clearances [54].

Arsenic, a metalloid, is one of the major groundwater contaminants which induces numerous health hazards including cardiotoxicity and affects the health of millions of people globally [102]. The mechanism of arsenic toxicity has been well established in both in vitro and in vivo. The epigenetic intervention of miRNAs in arsenic exposure is being explored with very few studies providing us a comprehensive understanding ([103] [116]. Humans are the most affected organisms by arsenic. Two studies focus on the miRNAs perturbations in humans exposed to arsenic. A study conducted by Pérez-Vázquez et al. [77] reported the negative association between arsenic toxicity and plasma miR-126 levels in children. However, the sample size was limited and had too many variables to provide any conclusive proofs. Chen et al. [97] instigated the relation between arsenic and miRNAs in adult females of Bangladesh origin. Bangladesh is one of the leading countries with high levels of arsenic contamination in groundwater. They found major miRNAs that might play a role in various cancer induction genes (miR-155, miR-338, miR-210).

3.3. Nanoparticles

Due to their advantageous physiochemical properties, nanoparticles (NPs) are elaborately used in various sectors including health and personal care products [104]. These NPs ultimately end up in the environment via various routes including air, water and soil leading to various ill-effects to biological systems. NPs enter cells via endocytosis or in ionic form inducing toxicity mainly by generating oxidative stress leading to apoptosis and inflammation [105]. miRNAs have been
identified to modulate the pathways involved in oxidative stress. Pulmonary inflammation induced by $\text{Al}_2\text{O}_3$ NPs was identified to be regulated by miR-297 in human bronchial epithelial cells by repression of NF-κB-activating protein which activates the notch signalling pathway [62]. Mn NPs have also been identified to induce an inflammatory response by targeting TNF-α and IL-6 through miR-155 in neuronal cells. The decrease in the miR-155 level in Mn NPs exposed cells led to an increase in mRNA levels of TNF-α and IL-6, which was validated by the transfection of miR mimics [45]. Nano polystyrene, a type of plastic widely used in personal care products, is one of the contaminants of emerging concern. Upon exposure to $C.\text{elegans}$, five altered major miRNAs were validated (miR-35, miR-38, miR-76, miR-354, and miR-794) using RNAi assay and were identified to be involved in various signalling pathways including the Wnt pathway [89]. Granulosa cells of hens, when exposed to Zn NPs, differential expression of miRNAs was found and they were predicted to play a major role in the normal development than the usual signalling cascades involved in NPs toxicity [47].

Nanosized $\text{SiO}_2$ induced lung damage in rats is due to the disturbance in the inflammatory signalling pathway. This was controlled by miRNAs as evinced by a decreased expression of PDCD4, an anti-inflammatory marker at the protein level, but with little significance in mRNA levels along with the increased expression. Moreover, the raised protein levels of LIN28B, CTGF promote fibrosis formation which is associated with miR-212 and miR-18a [76]. $\text{SiO}_2$ NPs have been shown to induce apoptosis via the death receptor pathway in murine spermatocyte cells. In this study, miR-2861 was shown to be repressed, which is increased in turn upregulates the mRNA levels of fas/fasl/ripk1/fadd [56]. Combinatorial effects of $\text{SiO}_2$ NPs along with methylmercury and lead acetate in zebrafish provides a pandect on the effects on miRNAs. Along with methylmercury, $\text{SiO}_2$ NPs have been demonstrated to reshape the miRNAs threshold (miR-7147, miR-26a and miR-375) in zebrafish embryos (48 hpf) leading to cardiovascular toxicity (i.e., cardiac muscle contraction) via inflammatory pathways [80]. Furthermore, in conjunction with lead acetate, $\text{SiO}_2$ NPs cause cardiac muscular contraction leading to cardiovascular toxicity. However, the impaired miRNAs were different and they were found to modulate alternate mechanisms including ER stress and disrupt calcium homeostasis [80].

Silver, iron and gold NPs are some of the most widely used NPs in medicine. All these NPs have been shown to induce toxicity and control gene expression via epigenetic mechanisms, especially by controlling miRNAs. Ag NPs exposure to human jurkat T cells has been shown to induce DNA damage and apoptosis. The miRNAs altered in a study carried out by Eom et al. underwent in silico prediction of miRNA-mRNA network analysis to identify putative pairs [32]. However, unless the prediction of miRNA targets is validated, it is difficult to obtain a conclusive evidence. A similar study was done by Oh et al. [41] in human embryonic stem cell-derived neural stem/progenitor cells showed that exposure to citrate-coated Ag NPs alters miRNAs involved in oxidative stress (especially Nrf2 mediated) and inflammatory pathways. Moreover, miR-297, which was previously shown to target NFKBAP in exposure to $\text{Al}_2\text{O}_3$ NPs, here was predicted to target ADAMTS9 and SEMA6D. When ciliates $E.\text{vannus}$ was exposed to Ag NPs, they showed similar ill effects including alteration in the cell cycle regulation, induced oxidative stress and antioxidant response modulation with over 15 miRNAs detected to play a possible action in the toxicity [85]. Research done by Huang et al. [38] in Au NPs upon exposure to human dermal fibroblasts showed the alteration of miRNAs prominently in the mRNA processing pathway, and MAPK signalling pathway. A key aspect of the finding is that Au NPs showed no cytotoxic effects even though they altered the levels of numerous miRNAs (i.e., miR-205, miR-21, miR-129 – 5p, miR-20a, miR-30b, miR-181a, miR-190, miR-16, miR-195, miR-30d, and miR-9) and affected the cell cycle pathway. SPIOns have been shown to induce cell death by targeting the NMDAR-Caspase pathway in PC12 cells leading to neurotoxicity. NMDAR, a receptor which regulates neuronal plasticity, was downregulated in SPIOns exposed cells and miRNAs has been shown to be varied [39]. A recent study compared the effect of three major NPs (i.e., Ag, Au, and SPIOns) in HepG2 cells where the similarity of miRNAs between treated NPs was very low. However, miRNAs altered in these NPs have been previously reported to play a role in cell proliferation and tumorigenesis [106]. An in-silico prediction by Hu et al. [107] identified six major miRNAs that have been found in response to various NPs exposure in zebrafish. These miRNAs include miR-124, miR-144, miR-148, miR-155, miR-19a, and miR-223. It is noteworthy that these miRNAs have been validated earlier in mammalian and zebrafish miRNAs Profiling studies and their predicted targets were found to be interacting with various signalling pathways (as reviewed by [107]). There is no regulation for the accumulation of NPs in the environment, which is of growing concern.

3.4. Biotoxins

Biotoxins are toxins produced by various organisms that have become a threat to human health and the environment. This includes but is not limited to mycotoxins, bacterial toxins, aflatoxins and plant toxins. MCs that are released by cyanobacteria and other algae are one of the major environmental toxins. MC-RR, one of the common and abundant MCs, has been shown to disrupt miRNAs expression in zebrafish embryos leading to cardiotoxicity. The loss of vascular integrity was predicted to be due to miR-31 and miR-126. Apart from these two miRNAs, numerous other miRNAs with known functions in multiple signalling pathways, were identified [65].

Upon exposure to mouse granulosa cells, MC-LR - a form of microcystin– has been shown to alter numerous miRNAs involved in MAPK signalling pathway [48,49]. In human liver cells, differential expression of miRNAs (i.e., miR-451a, miR-4521 and miR-15b-3p) leading to MC-LR induced hepatotoxicity was observed [76]. The same group further validated the role of miR-451a by using miR mimics and observed that the decreased expression of miR-451a by MC-LR is irreversibly [52]. This miR-451a plays a role in numerous signalling cascades and has also been shown to be functioning as circulatory miRNAs. In mice, the exposure to MC-LR- even at low dosages– induced non-alcoholic steatohepatitis (NASH), a common form of non-alcoholic fatty acid liver disease. Deregulation of miRNAs (i.e., miR-12, miR-21, miR-24 and miR-34a) has been identified as oncormis which leads to hepatocarcinogenesis in NASH [108]. The possible role of miR-541 in MC-LR –induced cell death was studied by Meng et al. [44] using miRNA mimics and inhibitors. They validated the downstream target of miR-541 (p15) in Mouse GC-1 cells by using a dual-luciferase-reporter assay which confirms the interaction between miR-541 and the 3′ UTR region of p15. p15, a CDK inhibitor, is one of the key players involved in cell cycle regulation. Inhibition of p15 by miR-541 leads to the cell death mechanism as evidenced by the findings of the study. Similarly, prenatal exposure to MC-LR in mice leads to ER stress and neuronal apoptosis in the hippocampal region of offspring leading to cognitive impairment. One of the key signalling regulators involved in ER stress is Gpr78/BIP, which acts as a chaperone, and was significantly upregulated in treated mice. This was due to the inhibition of miR-181a-5p upon MC-LR exposure, which was supported by the reporter assay [100]. MC-LR has been shown to induce liver toxicity in juvenile silver carp where the unbalanced miRNA levels play a crucial function. Furthermore, systemic toxicity in the carp was predicted due to the upregulation of four miRNAs (i.e., miR-16, miR-181a-3p, miR-223, miR-451) which are the key components of multiple signalling cascades [96].

Mycotoxins are secondary metabolites produced by the fungi and most of them have been found as contaminants in animal feed. These–when fed to animals–easily enter the human systems. They have been shown to have varied toxic potency such as mutagenicity, teratogenicity, neurotoxicity as well as carcinogenicity [129].

ZEA is a mycotoxin from $\text{Fusarium}$ genera that is one of the widely
prevailing toxins. Li et al. [61] investigated the regulatory mechanism of miRNA-ceRNA networks. It is one of the very few studies exploring miRNA-ceRNA networks upon xenobiotic exposure. They studied the effect of ZEA on porcine granulosa cells. Upon exposure to porcine granulosa cells, ZEA arrests the cell cycle at the G2/M phase by targeting the genes involved in the cell cycle including CDK1, CCNB1, CDC25A, and CDC25C. These genes are modulated by various miRNAs (i.e., miR-1839−3p, miR-1265a-3p, miR-15a, miR-152, miR-29b, miR-143−3p, and miR-7857−3p) which in turn are being controlled by various IncRNAs. These IncRNAs compete with miRNAs for binding towards these miRNAs, and fine tunes the miRNAs expression. However, the ceRNA hypothesis—which states that ceRNAs can compete with miRNAs for mRNA binding—is controversial and has to be validated further [109]. DON is another toxin of the same category, but more hazardous than ZEA [110]. The combinatory effect of ZEA and DON on the ascending colon of porcine showed an alteration of miRNAs (i.e., miR-15a, miR-21, miR-34a, and miR-192) involved in the cell cycle, signal transduction and apoptosis. However, the alteration of miRNAs was tissue-specific. The other tissues including liver did not show any significant changes [73].

Ochratoxin A, is a type of mycotoxin obtained from Aspergillus and Penicillium genera. It is considered as a potential carcinogen exhibiting severe toxicity. Marin et al. [90] reported that ochratoxin A alters miRNA levels in the kidneys of pigs with the identified miRNAs playing a major role in renal damage. The elevated miRNAs (i.e., miR-497, miR-133a-3p, miR-423−3p, miR-34a, miR-542−3p) and repressed miRNAs (i.e., miR-421−3p; miR-490; miR-9840−3p) were predicted for the pathways involved in the TP53 signalling cascade, a prominent pathway in tumorigenesis.

Apart from these mycotoxins, bacterial and plant toxins have also been reported to alter miRNAs. Staphylococcal Enterotoxin B produced by Staphylococcus aureus induces lung damage, and shown to be regulated by two major miRNAs (i.e., miR-222 and miR-494) which target CDKN1B, P27KIP1, and BCL2L11, some of the major genes involved in cell cycle [46]. Ricin, a highly potent toxin classified as a bioterror agent, is isolated from Ricinus communis. Mice, when intoxicated with ricin, show severe damage in the lungs. Transmuted miRNAs were identified in the lungs. These modified miRNA levels were found to have targets in various immune response and immune regulation pathways [94].

3.5. Particulate matter

Particulate matter (PM) is one of the major toxicants in air affecting more than 91 % of the people globally (as reported by WHO) [111]. They can cause various respiratory illnesses including lung cancer, COPD and even cardiovascular diseases. These toxicants are altering the epigenetic landscape [112]. PM2.5 has been shown to dysregulate the miRNAs involved in oxidative stress and inflammatory pathways [55]. Furthermore, it has been shown that it induces cardiotoxicity by altering miRNAs (i.e., miR-128−3p and miR-4306) in which miR-128−3p targets MAPK activity [57]. In zebrafish, PM2.5 has been shown to disrupt homeostasis of miRNA levels, upregulate the miRNAs involved in the inhibition of immune responses and DNA damage repair (i.e., let-7b, miR-153b-3p, miR-122 and miR-24) as well as to down-regulate miRNAs that control autophagy (i.e., let-7i, miR-19a-3p, miR-19b-3p and miR-7a) [79].

Cigarette smoking generates a large amount of particulate matter of various sizes which affects both first hand as well as second hand smokers [113]. A study conducted by Xi et al. [114] showed that in human respiratory epithelial cells, cigarette smoke condensate induces the expression of miR-31, one of the key oncomirs. Moreover, environmental cigarette smoke has been shown to dysregulate miRNA expression in both liver and lungs of mice with significant alterations in the lungs [115]. Maternal cigarette smoking is a major concern which affects the unborn child. It has been shown to affect the placenta by inhibiting the cell cycle regulation leading to improper placenta development. This is due to the suppression of miR-16, miR-21 and miR-146a in the placenta [64]. However, further studies are needed to address the environmental cigarette smoke (passive or second hand) and their role in miRNA regulation in human subjects.

3.6. Contaminants of emerging concern

Contaminants of emerging concern (CEC) are chemical compounds that are widely present in the environment with recent identification. While no common definition for this term exists, the present review focuses on major chemical compounds that can cause severe health effects in biological systems. Phthalates, is a family of phthalic acid diesters which exhibits endocrine disruption ability. Phthalates are being widely used along with plastics and pose a risk to human health. Scarano et al. [88] reported the effect of a mixture of phthalates from the environment in miRNA levels of pregnant rats. The altered miRNAome and the target prediction indicated that the majority of altered genes involved in inflammation and androgenic toxicity were modulated by miR-143-3p and miR-184.

Pesticides are another major CEC with an increased usage in agriculture. Atrazine is one of the more common herbicides used to prevent the growth of broadleaf and grassy weeds. In zebrafish, atrazine exposure altered miRNA levels that participate in various functions including angiogenesis. Wirbsky et al. have identified one key miRNA, namely miR-126−3p that was altered in various dosages [75]. The miR-126 family has been predicted to be involved in various toxicant exposures. The endocrine disrupting ability was further supported by a study done by Wang et al. [50]. In common carp, atrazine exposure at different developmental stages modulated the miRNAs involved in reproductive toxicity. Triclosan, one of the prevalent bactericides, affects the vascular development of zebrafish by upregulating miR-181a-5p levels involved in the phospholipid signalling pathway [87].

4. Challenges

There have been numerous studies on the interaction of miRNAs in various xenobiotics in both in vitro and in vivo of various model systems, including human subjects. However, they pose various challenges as well as limitations for the possible interpretation of data to environmental relevance. Most of the studies have focused on the identification of miRNAs altered through sequencing and predicted their targets in silico. Only very few of them have validated the interaction between miRNA and miRNAs and their role in gene regulation. Quantification of miRNA levels and in silico target prediction alone does not confirm their functional validation. Moreover, one of the interesting observations in xenobiotics-based studies is that though some of the miRNAs share the same pathways leading to toxicity, almost all of the altered miRNAs in various toxicants are different from each other, showing an increased specificity of these miRNAs. Even the similar miRNAs in different toxicant exposures have differed targets interacting with varied signalling pathways. The generalization of these results is very difficult at this stage due to their variability. The variables include dose, time, model systems, tissue specificity, toxicant characteristics and the method of analysis.

Most of the in vitro studies were done using cancer cell lines which might distort miRNAs alteration in normal functioning cells. Human studies have been very limited, and even in the few human studies that have been conducted, sample sizes were on the lower side and focused on a specific set of people. This does not contribute to a deeper understanding of the miRNAs effect on xenobiotic exposure. Furthermore, there are very limited studies that yield a conclusive evidence on the stability of miRNA alteration, whether it is transient or stable over generations.
5. Future directions

Future work should focus on the validation of predicted targets with high specificity and robust methods of identification that will help us in elucidating the exact mechanism of miRNA-xenobiotic perturbations. Meta-analysis of these studies will provide us an in-depth interpretation and comparison for generalization. Another interesting area of research includes miRNA-induced transcription activation and their possible mechanisms. Moreover, circulatory miRNAs and their role in xenobiotic exposure is very limited at this stage. It is one of the unexplored areas which promises an exciting future due to their applications as biomarkers useful in the identification of environmental toxicity. Furthermore, the controversy behind ceRNAs and miRNAs in gene regulation has to be ratified conclusively. Ligorio et al. (2011) predicted the Dicer to play a major role in xenobiotic targets, however there have not been many studies on the effect of toxicants in regulating miRNAs and their biogenesis[131]. These studies possess great potential in explaining xenobiotic toxicity and the possible role of miRNAs as biomarkers.

6. Conclusion

In conclusion, this review summarizes the effect of xenobiotics on gene expression via epigenetic regulation of miRNAs both in vitro and in vivo. Most xenobiotic toxicity is induced by the generation of oxidative stress, which leads to the dysregulation in antioxidant response, inflammation and other cell death mechanisms. These alterations are regulated by epigenetic modulation of miRNAs, which targets miRNAs and cause translational repression or degradation. Even with an increased amount of research going on, a lot of complex mechanisms behind miRNA regulation and its role in toxicity still remains largely unexplored.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to apologize to the researchers, whose work were not covered or cited in the review due to specific constraints and acknowledge their contributions. The authors thank the Department of Science and Technology, Science and Engineering Research Board - Empowerment and Equity Opportunities for Excellence in Science (EEQ/2018/000633) and RUSA 2.0-BEICH, Bharathiar University, Coimbatore.

References

[1] S. Mostafalou, M. Abdollahi, Pesticides and human chronic diseases: evidence, mechanisms, and perspectives, Toxicol. Appl. Pharmacol. 268 (2) (2013) 157–177. Apr 15.

[2] M.A. Burgos-Aceves, A. Cohen, G. Paolella, A.M. Burroughs, A.J. Carlisle, An integrated expression atlas of miRNAs and their promoters in human and mouse, Nat. Biotechnol. 29 (9) (2011) 872 Sep.

[3] Y. Yi, Q. Jin, J.G. Macara, Exportin-5 mediates the nuclear export of pre-miRNAs and short hairpin RNAs, Genes Dev. 17 (2003) 3011–3016 Dec 15.

[4] M.T. Bohnack, R. Capolino, D. GÖRLICH, Exportin-5 is a Ran-GTP-dependent mRNA-biding protein that mediates nuclear export of pre-miRNAs, RNA 10 (2004) 185–191 Feb 1.

[5] R.F. Ketting, S.E. Fischer, E. Bernstein, T. Sijen, G.J. Hannon, R.H. Plasterk, Dicer functions in RNA interference and in synthesis of small RNA involved in developmental timing in C. Elegans, Genes Dev. 15 (2001) 2654–2659 Oct 15.

[6] H. Kobayashi, Y. Tomari, RISC assembly: coordination between small RNAs and Argonaute proteins, Biochim. Biophys. Acta. (BBA)-Gene Regulatory Mechanisms 1859 (1) (2016) 71–81 Jan 1.

[7] J.J. Kim, Yoon H.J. Yu SY, S.Y. Lee, J.P. Youn, S.Y. Hwang, Epigenetic regulation of miR-22 in a BPA-exposed human hepatoma cell, Biochip J. 9 (1) (2015) 76–84 Mar 1.

[8] H. Guo, N.T. Ingolia, J.S. Weissman, D.P. Bartel, Mammalian microRNAs predominantly act to decrease target mRNA levels, Nature 466 (7308) (2010) 835–840. Aug.

[9] J. Zhang, W. Zhou, Y. Liu, T. Liu, C. Li, L. Wang, Oncogenic role of microRNA-532-5p in human colorectal cancer via targeting of the SULT3 of RUNX3, Oncol. Lett. 15 (5) (2018) 7215–7220 May 1.

[10] S.S. Truedsell, R.D. Mortensen, M. Seo, J.C. Schroeder, J.H. Lee, O. LeTouqueze, S. Vassudevan, MicroRNA-mediated mRNA translation activation in quiescent cells and oocytes involves recruitment of a nuclear microRN, Sci. Rep. 2 (2012) 842 Nov 13.

[11] A. Dharap, P.K. Prayuka, S. Murali, G. Pandi, R. Vemuganti, MicroRNA miR-324-3p induces promoter-mediated expression of RelA gene, PLoS One 8 (11) (2013).

[12] C. Baer, R. Claus, C. Plass, Genome-wide epigenetic regulation of miRNAs in cancer, Cancer Res. 73 (2013) 473–477 Jan 15.

[13] A. Thind, C. Wilson, Exosomal miRNAs as cancer biomarkers and therapeutic targets, J. Extracell. Vesicles 5 (1) (2016) 31292 Jan 1.

[14] L. Rossi, E. Benzamor, I. Farassati, Modification of miR-3 gene expression pattern in human colon cancer cells following exposure to 5-fluorouracil in vitro, Pharmacol. Res. 56 (3) (2007) 248–253 Sep 1.

[15] S. Paul, S.J. Kim, H.W. Park, S.Y. Lee, Y.R. An, M.J. Oh, J.W. Jung, S.Y. Hwang, Alteration in miRNA expression profiling with response to nontypophen in human cell lines, Cell 20 (2009) 0 Mar 31.

[16] H. Duan, Y. Jiang, H. Zhang, Y. Wu, MiR-320 and miR-494 affect cell cycles of primary murine bronchial epithelial cells exposed to benzo [a] pyrene, Toxicol. Vitr. 24 (3) (2010) 928–935. Apr 1.

[17] J. Bolley, J. Fraczek, M. Vinken, D. Lizarraga, S. Gaj, J.H. van Delft, V. Rogiers, T. Vanhaecke, Effect of Trichostatin A on miRNA expression in cultures of primary rat hepatocytes, Toxicol. Vitr. 25 (6) (2011) 1173–1182 Sep 1.

[18] J. Bolley, S. Gaj, K.J. Bruers, L. Timmermans, J.C. Kleinjans, J.H. van Delft, Benzo [a] pyrene-induced changes in MicroRNA-mRNA networks, Chem. Res. Toxicol. 25 (4) (2012) 838–849. Apr 16.

[19] L. Xu, W. Qin, H. Zhang, Y. Wang, H. Dou, D. Yu, Y. Ding, L. Yang, Y. Wang, Alterations in microRNA expression linked to microcytosis-Li-induced tumorigenicity in human WRL-68 Cells, Mutat. Res. Toxicol. Environ. Mutagen. 743 (1–2) (2012) 75–82 Mar 18.

[20] T.F. Lo, W.C. Tsai, T.S. Chen, MicroRNA-21-23p, a berberine-induced microRNA, directly down-regulates human melanoma adenocarcinoma 2A and 2B and inhibits hepatoma cell growth, PLoS One 8 (9) (2013).

[21] M.K. Song, H.S. Choi, H.S. Lee, Y.J. Kim, Y.K. Park, J.C. Ryu, Analysis of microRNA and mRNA expression profiles highlights alterations in modulation of the MAPK pathway under octanol exposure, Environ. Toxicol. Pharmacol. 37 (2014) 84–94 Jan 1.

[22] K. Takahashi, N. Tatsumi, T. Fukumi, T. Yokoi, M. Nakajima, Integrated analysis of rafampicin-induced microRNA and gene expression changes in human hepatocellular carcinoma, Drug Metab. Pharmacokinet. (2014) DMPK-11.

[23] H.J. Eom, N. Chatterjee, J. Lee, J. Choi, Induced miRNA and mRNA microRNA profiling reveals epigenetic mechanism of differential sensitivity of Jurkat T cells to AgNPs and Ag ions, Toxicol. Lett. 228 (1) (2014) 211–218 Jun 17.

[24] Q. Yang, E. Xu, J. Dai, E. Bie, X. Zhang, B. Peng, J. Chuang, J. miR-21 regulates N-methyl-N-nitro-N-nitrosoguimidine-induced gastric tumorigenesis by targeting FASLG and BTG2, Toxicol. Lett. 228 (3) (2014) 147–156 Aug 4.

[25] D. Tawosri, Y. Yan, J.M. Olson, Z.J. Bongjik, B. Xiao, Down-regulation of microRNA-21 is involved in the propofol-induced neurotoxicity observed in human stem cell-derived neurons, Anesthesiology. J. Am. Soc. Anesthesiolog. 121 (4) (2014) 786–800 Oct 16.

[26] C.V. Segal, C. Koufariotis, C. Powell, N.J. Gooderham, Effects of treatment with
androgen receptor ligands on microRNA expression of prostate cancer cells, Toxicology 333 (2015) 45–52 Jul 3.

[36] P. Su, F. Zhao, Z. Cao, J. Zhang, M. Aschner, W. Luo, Mir-203-modulated tricellulin mediates lead-induced intracellular apoptosis through inhibition of Prohibitin and Nrf2, Toxicology 414 (2018) 1–10 Oct 17.

[37] C. Liu, H. Guo, X. Cheng, M. Shao, C. Wu, H. Li, W. Tan, S. Cheng, Exposure to airborne PM2.5 suppresses microRNA expression and degrades target oncogenes that cause neoplastic transformation in NIH3T3 cells, Oncotarget 6 (2015) 29448–29458 Oct 6.

[38] Y. Huang, L. Qi, Q. Yu, S. Wu, MicroRNA sequencing and molecular mechanisms analysis of the effects of gold nanoparticles on human dermal fibroblasts, Materials 35 (2015) 13–24 Jan 31.

[39] B. Sun, R. Liu, N. Xu, Y.-Y. Xia, Comprehensive evaluation of microRNA expression profiling reveals the neural signaling specific cytotoxicity of superparamagnetic iron oxide nanoparticles (SPIONs) through N-Methyl-D-aspartate receptor, PLoS One 10 (3) (2015).

[40] A.K. Marrone, V. Tryndyak, F.A. Beland, I.P. Pogribny, MicroRNA responses to the genotoxic carcinogens aflatoxin B1 and benzo[a]pyrene in human HepG2 cells, Toxicol. Sci. 149 (2) (2016) 496–502 Feb 1.

[41] J.H. Oh, M.Y. Son, M.S. Choi, S. Kim, A.Y. Choi, H.A. Lee, K.S. Kim, J. Kim, C.W. Song, S. Yoon, Integrative analysis of genes and microRNA alterations in human embryonic stem cells-derived neural cells after exposure to silver nanoparticles, Toxicol. Appl. Pharmacol. 299 (2016) 8–23 May 15.

[42] Y. Yanamata, M. Asakura, R. Mizugishi, H. Fujii, K. Nagei, A. Aruda, T. Isho, R. Fujuwara, MicroRNA expression in the vildaplatin-treated two-and-three-dimensional HepG2 cells, Drug Metab. Pharmacokinet. 31 (2016) 201–209 Jun 1.

[43] J. Oeharto, A. Karababa, M. Castoldi, H.J. Bidmon, B. Görg, D. Häussinger, X. Meng, L. Zhang, X. Chen, Z. Xiang, D. Li, A new role for microRNA miR-541 contributes to Jun-mediated inhibition of the pro-inflammatory response pro-miR-15a and pro-miR-16, Toxicology 385 (2017) 173–174 Nov 1.

[44] D.M. Elliott, P.S. Nagarkatti, M.H. Jeong, I.J. Bang, H.R. Kim, K.H. Chung, MicroRNA regulatory networks repress transcription pro-miR-16 and pro-miR-15a in mouse liver during pregnancy is associated with downregulation of miR-16, miR-21, and miR-146a in the placenta, Epigenetics 5 (2010) 583–589 Oct 1.

[45] Y. Zhao, Q. Xiong, P. Xie, Analysis of microRNA expression in embryonic development toxicity induced by MC-R, PLoS One 6 (7) (2011).

[46] W. Yoshioka, W. Higashiyama, C. Tohyma, Involvement of microRNAs in dioxin-induced liver damage in the mouse, Toxicol. Sci. 122 (2011) 457–465 Aug 1.

[47] Y. Zhao, P. Xie, H. Fan, Genomic profiling of microRNAs and proteins reveals an early molecular alteration associated with tumorigenesis induced by MC-LR in mice, Environ. Sci. Technol. 46 (1) (2012) 34–41 Jan 3.

[48] M.J. Jenny, N. Aluru, M.E. Hahn, Altered microRNA expression in the cervix during pregnancy associated with lead and mercury exposure, Epigenomics 6 (2014) 805–896 Sep 1.

[49] B. De Felice, F. Manfioletto, P. Albuimo, J. Troisi, F. Zullo, C. Di Carlo, D.A. Sardo, N. De Stefano, U. Ferbbo, M. Guida, M. Guida, Genome-wide microRNA expression profiling in placenta from pregnant women exposed to BPA, BMC Genomics 15 (2014) 1–17 Oct 1.

[50] A.P. Sanders, H.H. Burris, A.C. Just, V. Motta, C. Amarasingravenda, K. Svensson, E. Oken, M. Solano-Gonzalez, A. Mercado-Garcia, I. Panic, J. Schwartz, Altered miRNA expression in the cervix during pregnancy associated with lead and mercury exposure, Epigenomics 7 (2015) 24 Jan 1.

[51] P. Brzuzan, M. Woźny, Ł. Wolfska-Nizioł, A. Piaszek, M. Florczyk, E. Jakimik, M. Góra, M.K. Łuczynski, M. Gajecki, MicroRNA expression profiles in liver and colon of sexually immature gifts after exposure to Fumoxmcis, Pol. J. Vet. Sci. 18 (1) (2015) 29–38 Mar 1.

[52] A. Nan, X. Zhou, L. Chen, M. Liu, N. Wang, Z. Yang, L. Luo, Z. Liu, L. Dai, Y. Jiang, A transcribed unconserved noncoding RNA, Uc. 173, is a key molecule for inhibition of lead-induced neuronal apoptosis, Oncotarget 7 (2016) 112 Jan 5.

[53] S.E. Wirbisky, G.J. Weber, K.E. Schlotman, M.S. Sepúlveda, J.L. Freeman, Embryonic atraxine exposure alters zebrafish and human miRNAs associated with angiogenesis, cancer, and neurodevelopment, Food Chem. Toxicol. 98 (2016) 25–33 Dec 1.

[54] H. Yang, Y. Zhang, W. Li, C. Lao, M. Li, Y. Zheng, Altered microRNA expression profiles in lung damage induced by nanosed SO2, Bioengineered 8 (2017) 11–22 Oct 1.

[55] M.S. Pérez-Vázquez, A.C. Ochoa-Martínez, T. Rulz-Vera, Y. Araiza-Gambao, L. Pérez-Maldonado, Evaluation of epigenetic alterations (mir-126 and mir-155 expression levels) in Mexican children exposed to inorganic arsenic via drinking water, Environ. Sci. Pollut. Res. Int. 24 (36) (2017) 28036–28045 Dec 1.

[56] F.V. Hassanian, S. Mehr, A. Bious, R. Birner-Gruenberger, H. Hosseinzadeh, Protective effect of crocin on BPA-induced liver toxicity in rats through inhibition of oxidative stress and downregulation of MAPK and MAPKAPK signaling pathway pro-MAPK, Int. J. Pharm. 479 (2015) 94–97 Jun 1.

[57] I. Veerapan, S.K. Sankaranwaran, R. Palasinam, M. Protects Humans Respiratory Cells from Direct and Induced Genotoxicity by Mitigating ROS and Reversing Altered microRNA Expression, Int. J. Environ. Res. Public Health 16 (13) (2019) 2839 Jan 1.

[58] L. Ren, J. Zhang, J. Wang, J. Wei, J. Li, X. Yu, Y. Li, C. Guo, J. Duan, Z. Sun, Silica nanoparticles induce spermatoocyte cell apoptosis through microRNA-2821 targeting death receptor pathway, Biosphere 228 (2019) 709–720 Aug 1.

[59] F. Wang, Q.W. Wang, Y.J. Zhao, Q.Y. Du, Z.J. Chang, Effects of short-time exposure to atrazine on microRNA expression profiles in the gonad of common carp, Chemosphere 194 (2018) 594–605 Aug 1.

[60] S. Balasubramanian, et al. Toxicology Reports 7 (2020) 583–595.
S. Balasubramanian, et al.

Toxicology Reports 7 (2020) 583–595

J. Liu, Y. Huang, F. Cai, Y. Dang, C. Liu, J. Wang, MicroRNA-181a regulates endoplasmic reticulum stress in oocytes exposed to arsenic-contaminated drinking water, Environ. Pollut. 259 (2020) 129607 1 May 1.

Q. Deng, X. Dai, W. Feng, S. Huang, Y. Yuan, Y. Xiao, Z. Zhang, N. Deng, H. Deng, X. Zhang, D. Kuang, Co-exposure to metals and polyyclic aromatic hydrocarbons, microRNA expression, and early health damage in coke oven workers, Environ. Int. 122 (2019) 369–380 Jan 1.

J. Ma, X. Chen, G. Xin, X. Li, Chronic exposure to the ionic liquid [C8mim][Br] induces inflammation in silver carp spleen: involvement of oxidative stress-mediated p38MAPK/NF-κB signalling and microRNAs, Fish Shellfish Immunol. 84 (2019) 627–638 Jan 1.

W.R. Scaraon, A. Bedrat, L.G. Alonso-Costa, A.M. Aquino, B.E. Fantinatti, L.A. Justulin, L.F. Barbisan, P.P. Freire, J.A. Flaws, B. Lemos, Exposure to an environmentally relevant phosphate mixture during prostate development induces microRNA upregulation and transcriptome modulation in rats, Toxicol. Sci. 171 (1) (2019) 84–97 Sep 1.

M. Qiao, L. Luo, Y. Yang, Y. Kong, D. Wang, Nanopollutant-induced microRNAs response in Caenorhabditis elegans after long-term and dose-loss exposure, Sci. Total Environ. 697 (2019) 13413Dec 20.

D.E. Marin, C. Braicu, G. Dumitrescu, G.C. Pistol, R. Cojocneanu, I.B. Neagoe, L. Feng, X. Yang, S. Liang, Q. Xu, M.R. Miller, J. Duan, Z. Sun, Silica nanoparticles exposure, Chemosphere (240) (2020) 124905Feb 1.

D.E. Marin, C. Braicu, G. Dumitrescu, G.C. Pistol, R. Cojocneanu, I.B. Neagoe, L. Feng, X. Yang, S. Liang, Q. Xu, M.R. Miller, J. Duan, Z. Sun, Silica nanoparticles exposure, Chemosphere (240) (2020) 124905Feb 1.

A. Wei, N. Patel, A. Rahman, Z. Stubbs-Russell, Cadmium nephrotoxicity is associated with altered microRNA expression in the rat renal cortex, Toxicol. 6 (1) (2018) 16 Mar 1.

Y. Pan, W. Zhang, S. Lin, Transcriptomic and microRNAomic profiling reveals molecular mechanisms to cope with silver nanoparticle exposure in the ciliate Euglotes vanneurii, Environ. Sci. Nano 5 (12) (2018) 2921–2935.

Q. Deng, X. Dai, W. Feng, S. Huang, Y. Yuan, Y. Xiao, Z. Zhang, N. Deng, H. Deng, X. Zhang, D. Kuang, Co-exposure to metals and polyyclic aromatic hydrocarbons, microRNA expression, and early health damage in coke oven workers, Environ. Int. 122 (2019) 369–380 Jan 1.

J. Ma, X. Chen, G. Xin, X. Li, Chronic exposure to the ionic liquid [C8mim][Br] induces inflammation in silver carp spleen: involvement of oxidative stress-mediated p38MAPK/NF-κB signalling and microRNAs, Fish Shellfish Immunol. 84 (2019) 627–638 Jan 1.