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REVIEW ARTICLE

Circulating microRNAs as biomarkers of environmental exposure to polycyclic aromatic hydrocarbons: potential and prospects

Rupa Rani[1] · Abhidha Kela[1] · Geeta Dhaniya[2] · Kamini Arya[1] · Amit K. Tripathi[3,4] · Rajesh Ahirwar[1]

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Abstract

Exposure to polycyclic aromatic hydrocarbons (PAHs) produced from various pyrogenic and petrogenic sources in the environment has been linked to a variety of toxic effects in the human body. Genome-wide analyses have shown that microRNAs (miRNAs) can function as novel and minimally invasive biomarkers of environmental exposure to PAHs. The objective of this study is to explore miRNA signatures associated with early health effects in response to chronic environmental exposure to PAHs. We systematically searched Scopus and PubMed databases for studies related to exposure of PAHs with changes in miRNA expression patterns that represent early health effects in the exposed population. Based on previous studies, we included 15 cell-based and 9 each of animal model and human population-based studies for assessment. A total of 11 differentially expressed PAH-responsive miRNAs were observed each in two or more cell-based studies (miR-181a and miR-30c-1), animal model studies (miR-291a and miR-292), and human population-based studies (miR-126, miR-142-5p, miR-150-5p, miR-24-3p, miR-27a-3p, miR-28-5p, and miR-320b). In addition, miRNAs belonging to family miR-122, miR-199, miR-203, miR-21, miR-26, miR-29, and miR-92 were found to be PAH-responsive in both animal model and cell-based studies; let-7, miR-126, miR-146, miR-30, and miR-320 in both cell-based and human population-based studies; and miR-142, miR-150, and miR-27 were found differentially expressed in both animal model and human population-based studies. The only miRNA whose expression was found to be altered in all the three groups of studies is miR-34c. Association of environmental exposure to PAHs with altered expression of specific miRNAs indicates that selective miRNAs can be used as early warning biomarkers in PAH-exposed population.

Keywords Polycyclic aromatic hydrocarbons (PAHs) · MicroRNAs · DNA damage · Genotoxicity · Oxidative stress

Highlights
- Differentially expressed miRNAs in cells, animal, and human studies were reviewed.
- Association of miRNA alteration, PAH exposure, and resulting adverse health effects is assessed.
- Common miRNA signatures among cells, animal, and human studies are identified.

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✉ Rajesh Ahirwar
r.ahirwar.nireh@gov.in

[1] Department of Environmental Biochemistry, ICMR-National Institute for Research in Environmental Health, Bhopal 462030, India

[2] Division of Endocrinology, CSIR-Central Drug Research Institute, Lucknow 226031, India

[3] Department of Molecular Biology, ICMR-National Institute for Research in Environmental Health, Bhopal 462030, India

[4] Present address: Department of Biotechnology, New Delhi 110003, India

Introduction

Polycyclic aromatic hydrocarbons (PAHs) are organic compounds composed of multiple fused aromatic rings bonded in the linear, cluster, or angular arrangements and do not contain hetero atom or substituents (Sahoo et al. 2020; Lawal 2017). PAHs with two to four rings are less soluble in water but more volatile and thus exist predominantly in gaseous form. PAHs with five or more rings are less soluble and have low volatility which accounts for their predominance in solid forms such as bound to particulates present in the soil, air, or sediment (Sahoo et al. 2020; Choi et al. 2010) (Fig. 1). PAHs are primarily generated from natural sources such as coal, wood, crude oil, forest fire, and petrol and mainly produced from anthropogenic processes such as industrial processes (e.g., coke manufacturing, power plants, and industrial boilers), residential heating (e.g., coal, wood, oil), open burning (e.g., forest and agricultural fires), and vehicles (gasoline and diesel engines). Thus, PAHs are

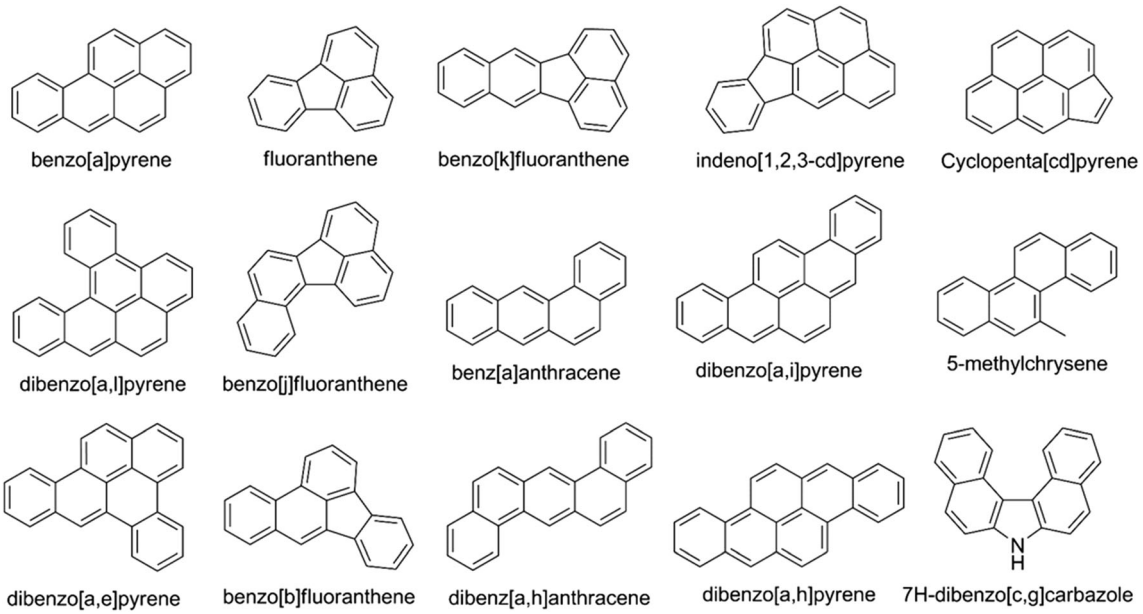

Fig. 1 Chemical structure of potentially carcinogenic PAHs to human

considered ubiquitous in the environment as both natural and anthropogenic activities increase their level in the ecosystem (soil, food, air, and water) (Deng et al. 2019; Abdel-Shafy and Mansour 2016).

PAHs are persistent in nature which leads to their exposure to human through inhalation, ingestion, and dermal contacts. Exposure to PAHs may result in adverse health effects due to their genotoxicity and carcinogenicity, immunotoxicity, and teratogenicity (Table 1). Sources of PAH exposure include industrial emissions (combustion of fossil fuels such as gas, oil, and coal), agricultural emission (e.g., during open burning of brushwood, straw, and stubble), ambient air (domestic solid fuel burning, combustion of fossil fuels, cigarette, and tobacco smoke), water (industrial effluents and accidental spills during oil shipment at sea), soil (airborne fallout, near oil refineries), foodstuffs (charring meat or barbecuing food over charcoal or wood), and recycling activities (e.g., e-waste dismantling and processing) (Rengarajan et al. 2015; Ahirwar and Tripathi 2021). Everyday-life exposure to PAH results in the formation of anti-benzo[a]pyrene diolepoxide adduct which leads to reduction of leukocyte telomere length and mitochondrial DNA copy number (Pavanello et al. 2020; Marriset al., 2020). Being lipophilic in nature, PAH internalization into cells via passive diffusion leads to the induction of cytochrome P450 (CYP) monooxygenases such as CYP1A1/2 and 1B1 and enzymes such as epoxide hydrolases, UDP glucuronyl transferases, glutathione S-transferases, NADPH quinone oxidoreductases, and aldo-keto reductases (AKRs) resulting in the biotransformation of PAHs into active carcinogens (radical cations, diolepoxides, and o-quinones). These metabolites react with DNA to produce PAH-DNA adducts and cause DNA mutation, chromosomal aberrations, abnormal gene expression, and genetic instability leading to tumorigenesis (Moorthy et al. 2015) (Fig. 2). PAH exposure causes oxidative stress, liver and kidney damage, and increased risk of cancers of the skin, lung, bladder, breast, and stomach (Deng et al. 2014a; Kim et al. 2013; Armstrong et al. 2004; Bostrom et al. 2002; Burchiel and Luster 2001). Leachi et al. (2020) undertook a descriptive review and reported that several studies exhibited that exposure to PAHs was associated with respiratory disorders such as asthma, chronic obstructive pulmonary disease, pulmonary wheezing, and cardiovascular diseases such as chest tightness and heart rate variation, increased blood pressure, and ischemic heart disease, respectively. Kuang et al. (2013) reported that presence of urinary monohydroxy PAHs and plasma benzo[a]pyrene-r-7,t-8,t-9,c-10-tetrahydotetrol-albumin (BPDE-Alb) adducts is associated with significant increase in oxidative damage to DNA and lipids result in chromosome aberrations and genetic instability. Considering their substantial genotoxicity to humans, the International Agency for Research on Cancer (IARC) and Environmental Protection Agency (EPA) have listed multiple PAHs such as benz[*a*]anthracene, dibenz[*a,h*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, benzo[*j*]-fluoranthene, benzo[*a*]pyrene, dibenzo[*a,e*]pyrene, dibenzo[*a,h*]-pyrene, dibenzo[*a,l*]pyrene, dibenzo[*a,i*]pyrene, indeno[1,2,3-cd]pyrene, 7H-dibenzo[*c,g*]carbazole, and 5-methylchrysene into categories, such as "probable," "possible," and "known carcinogens" to humans (IARC 2010). Thus, adverse health effects due to environmental exposure to polycyclic aromatic hydrocarbons are a major public health concern.

MiRNAs are endogenous, short, single-stranded non-coding RNAs that function as gene regulators at the post-transcriptional level by binding with target mRNAs at the 3′-untranslated regions (UTRs), which leads to translational

Table 1 Toxic effects of polycyclic aromatic hydrocarbons (PAHs)

Toxicity	Effects	References
Acute toxicity	Eye irritation, nausea, vomiting, diarrhea, confusion, skin irritation, and inflammation	Abdel-Shafy and Mansour (2016)
Carcinogenicity	Long-term exposure of PAHs is associated with increased risk of cancer of the lung, skin, esophagus, colon, pancreas, and bladder.	Tong et al. (2018); US-EPA (2008)
Immunotoxicity	Inhibition of pre B-, pre T-, and myeloid cell development, B- and T-cell suppression, apoptosis of lymphoid tissues, disruption of myelopoiesis, and altered cytokine production by macrophages and monocytes	Marriset et al. (2020); Rengarajan et al. (2015); Burchiel and Gao (2014); Burchiel and Luster (2001)
Genotoxicity	Exposure to PAHs and their reactive intermediates (e.g., diolepoxides, quinones, hydroxyalkyl derivatives) may lead to biochemical disruptions and cell damage resulting in mutations, developmental malformations, tumors, and cancer	Ramesh et al. (2010)
Teratogenicity	Exposure to PAHs during pregnancy has been associated with adverse birth outcomes, low IQ in children, increased behavior problems, and childhood asthma	Bolden et al. (2017); Edwards et al. (2010); Perera et al. (2005)

repression or degradation of mRNAs (Sisto et al. 2019). By impacting the expression levels of multiple mRNA targets, miRNAs regulate cellular, physiological, and pathological processes such as cellular growth and death, development and differentiation, endocrine homeostasis, and carcinogenesis (Peng and Croce 2016; Cheng et al. 2005; Chen et al. 2004). MiRNA genes located in the intergenic regions are transcribed predominantly by RNA polymerase II to produce several kilobases long stem loop structures (primary miRNA transcript or pri-miRNA) which are then cleaved by the Drosha–DGCR8 (Pasha) complex to release 60–70 nucleotide hairpin structures (precursor miRNA or pre-miRNA) for export to the cytoplasm through the nuclear pore by the Exportin-5–Ran-GTP. In the cytoplasm, the pre-miRNA is further processed by Dicer protein generating intermediary miRNA duplex, of which one strand is loaded onto the RNA-induced silencing complex (RISC) to form mature miRNA, where it guides RISC to silence target mRNAs through mRNA cleavage, translational repression, or deadenylation (Fig. 3A). While majority of the cellular miRNAs resides within cells, a small proportion of them is also released into the extracellular space via microvesicles and has been shown to function in various physiological and pathological processes (Weiland et al. 2012) (Fig. 3B). Recent studies have shown that these extracellular circulating miRNAs can persist in cell-free environments for a considerably longer period so that they can be used as diagnostic and prognostic biomarkers in multiple diseases such as cancers, diabetes, autoimmunity, and cardiovascular diseases (Schwarzenbach et al. 2014). For instance, the extracellular vesicles can be detected in body matrices like blood, exhaled breath condensates, bronchoalveolar lavage fluid, and urine making them valuable matrices for assessing miRNAs. In epidemiological research, these cell-free extracellular miRNAs present in minimally invasive body matrices (e.g., blood, plasma) have been recently acknowledged as biomarkers of environmental exposure to hazardous substances (Sisto et al. 2019; Berezikov 2011). Growing evidence shows that exposure to PAHs can alter the expression levels of microRNAs (miRNAs), mainly through p53-miRNA interaction in response to DNA damage, precursor microRNA-carcinogen adduct formation, and alterations of Dicer function (Izzotti and Pulliero 2014; Deng et al. 2014a; Jardim et al. 2009; Schembri et al. 2009) (Fig. 3C). The altered expression of miRNAs can lead to change in expression of various structural and functional proteins.

Several studies have predicted the diagnostic or therapeutic potential of a few miRNA candidates; however, review articles that critically or systematically assess the potential of PAH-responsive miRNAs as early warning effect biomarkers of PAHs exposure are scarce in literature. In the present article, an attempt has been made to review miRNA candidates and assess their potential as early warning signatures to PAH-induced health effects. This review examines the potential of circulating miRNAs as biomarkers of PAH exposure by reviewing epidemiological, in vivo, and in vitro studies reporting differential expression of miRNAs in response to environmental exposure to PAHs along with its observable impact on cellular or physiological processes.

Materials and methods

We developed a review protocol to include selected cell-based, animal model-based, and human population-based studies meeting the following inclusion criteria: (i) reported changes in miRNA expression levels upon exposure to PAH, (ii) the study was published in a peer-reviewed journal and reported original research, and (iii) the study reported association of PAH-induced altered miRNAs or their levels with

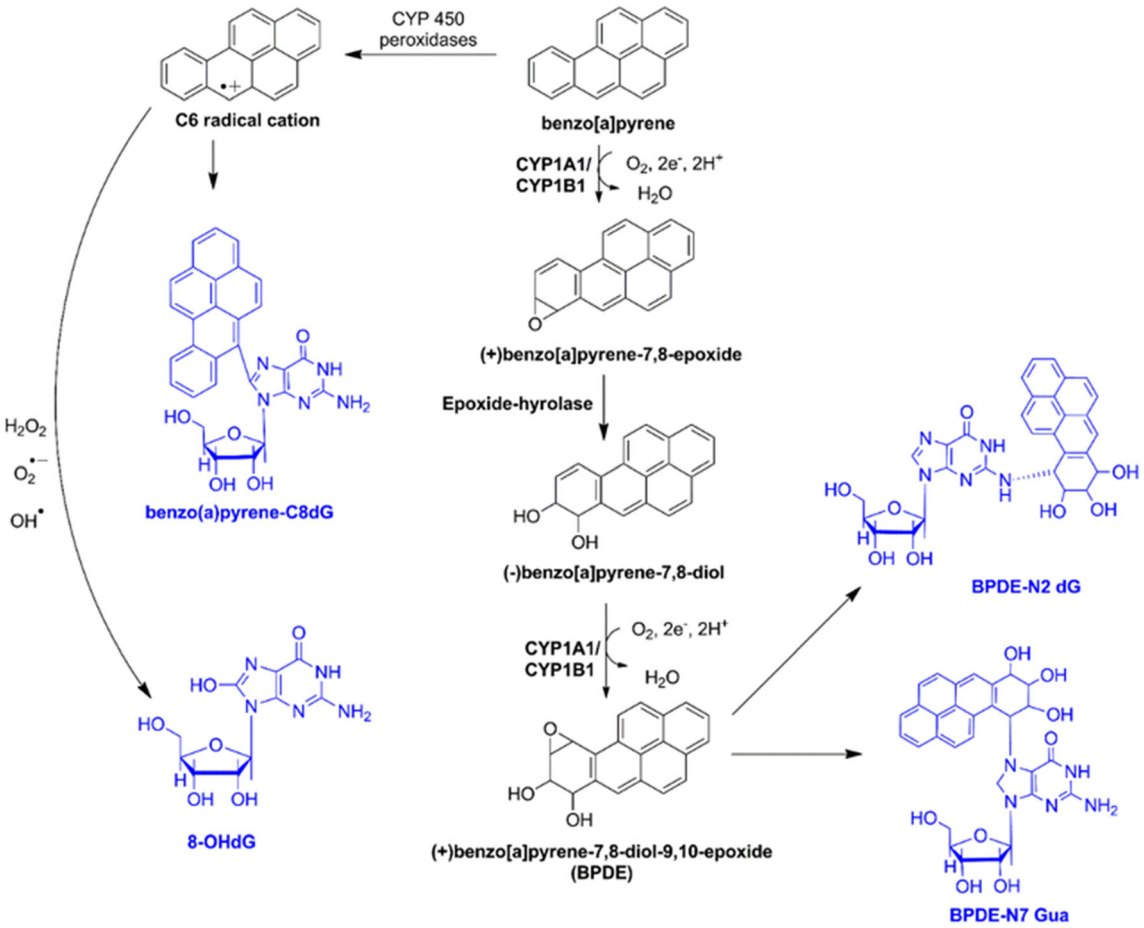

Fig. 2 Overview of PAH metabolism by mammalian cytochrome P450 enzymes (black) and generation of DNA adducts (blue) (Sources: Peng et al. (2008) and Godschalk et al. (2003)).

subsequent cellular/morphological changes (altered protein expression and/or enzymatic activity, DNA/chromosomal damage, increased oxidative stress, heart rate variability) representing early health effects in cells derived from human tissues, animal models, or human beings.

To identify relevant articles, we searched PubMed and Scopus databases using all possible combinations of keywords "miRNA," "microRNAs," "MiR," "mir" and "Polycyclic aromatic hydrocarbons," "PAHs," "anthracene," "pyrene," "fluoranthene," "chrysene," etc. in the article title and abstract of published studies, covering all previous years until February 2021 (Supplementary Information; Table 1).

Results

A total of 773 research articles were obtained through searching two of the most popular databases, i.e., PubMed and Scopus. Manual curation of the results lead to selection of 33 research articles in which at least one PAH compound was accurately quantified and the corresponding alteration in miRNA levels and physiological and biological changes corresponding to early health effects were assessed (Fig. 4). Studies providing non-validated miRNA changes in response to PAH exposure and/or those predicting putative targets or cellular roles of miRNAs based on in silico analyses were excluded due to lack of experimental validation (Supplementary Information; Tables 2 and 3).

All the included studies were grouped into in vitro, in vivo, and epidemiological study groups based on the type of exposed population. This includes 15 studies on cell-based systems (in vitro) and 9 each of animal models (in vivo) and human population (epidemiological)-based studies. The in vitro and in vivo studies reported the effect of controlled PAH exposure on miRNA expression levels and associated parameters in cell lines and animal models, respectively, whereas the studies on human population (epidemiological studies) assessed altered miRNA signatures in the population exposed to a mixture of pollutants carrying varying levels of PAHs from the ambient environment.

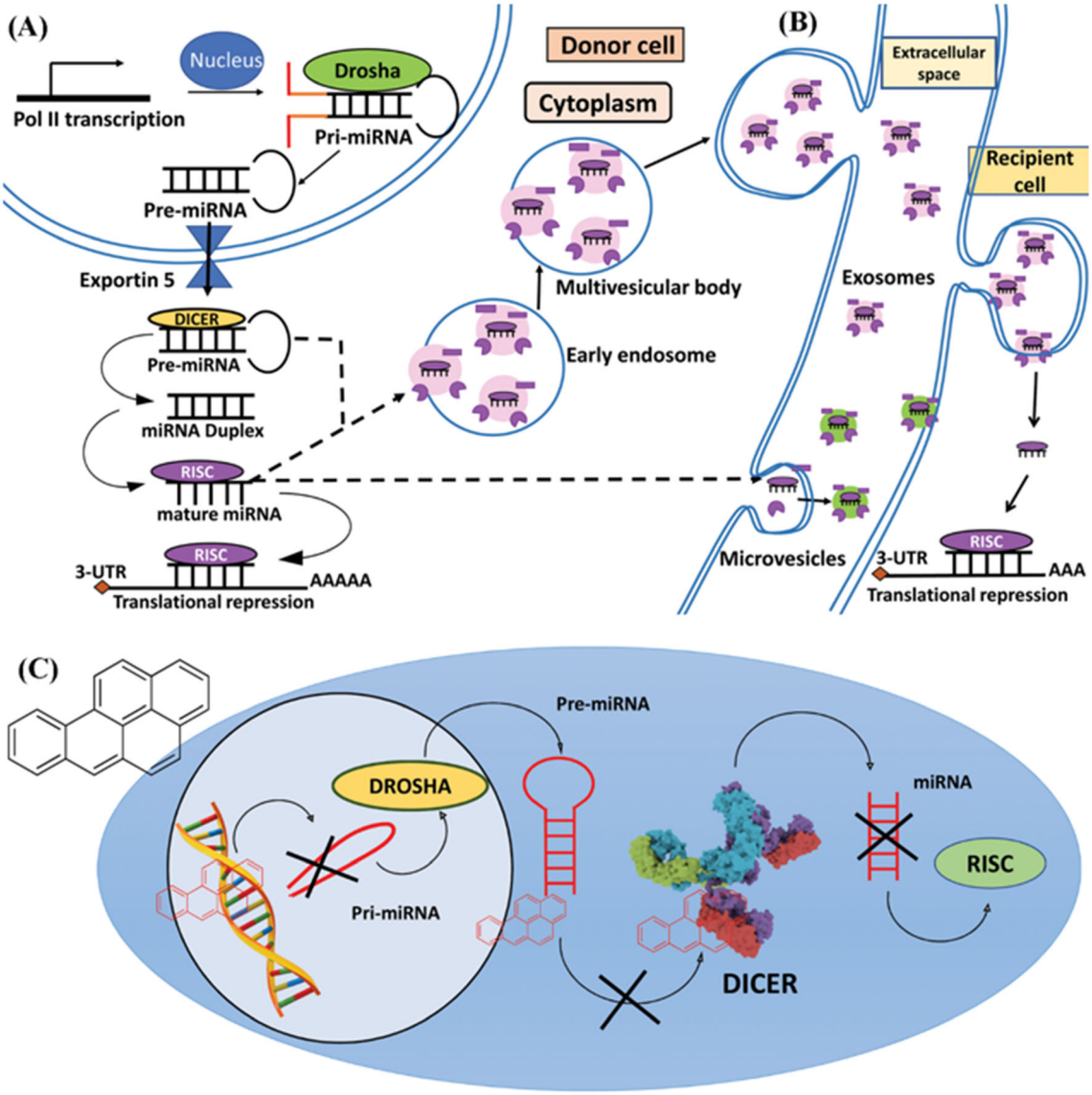

Fig. 3 Overview of miRNA biogenesis and mechanism of alteration of its expression by environmental pollutants. **A** MiRNA genes located in the intergenic regions are transcribed predominantly by RNA polymerase II to produce several kilobases long stem loop structures (primary miRNA transcript or pri-miRNA) which are then cleaved by the Drosha–DGCR8 (Pasha) complex to release 60-70 nucleotides (nt) hairpin structures (precursor miRNA or pre-miRNA) which are exported to the cytoplasm through nuclear pore by the Exportin-5–Ran-GTP (Lee et al. 2002). In the cytoplasm, the pre-miRNA is further processed by Dicer protein generating intermediary miRNA duplex, of which one strand is loaded onto the RNA-induced silencing complex (RISC) to form mature miRNA, where it guides RISC to silence target mRNAs through mRNA cleavage, translational repression, or deadenylation. **B** A fraction of the mature miRNAs can be released to the extracellular space via microvesicles which are shed from the plasma membrane into circulation or can be loaded into the multivesicular bodies which are docked onto the cell membrane to release positive exosomes into the extracellular space and find their way into serum and other biological fluids. **C** Mechanism of alteration of miRNA expression by PAHs (and other carcinogens) via p53/miRNA interaction and formation of adducts with miRNA (Izzotti and Pulliero 2014). **A** and **B** are reproduced from Chen et al. (2017), under a creative common attribution license (CCBY).

PAH-responsive miRNA signatures in cell-based studies (in vitro)

Benzo[a]pyrene (B[a]P), a five-ringed benzenoid formed of a benzene ring fused to a pyrene ring (Fig. 1) that is a PAH, is well studied in cell-based systems. The classical pathway of B[a]P-mediated carcinogenicity involves oxidative degradation of PAHs by cytochrome P450 enzymes (CYP1A1 and CYP1A2), converting them to electrophilic epoxides that can bind to DNA to form adducts and induce mutational hot spots in the DNA (Pogribny 2019). Several studies have reported B[a]P-associated genotoxicity which is partly responsible for its tumorigenicity as well as the effects of role of miRNAs in cell transformation induced by B[a]P. Chanyshev et al. (2019) investigated the exposure of B[a]P on mRNAs and their target miRNAs, miR-16, miR-17, miR-21, miR-27a, miR-126, miR-

Table 2 Cell-based studies on differential expression of miRNA upon exposure to PAHs

Cell lines	Pollutant	Affected miRNAs	Cellular/molecular changes	References
Primary cell cultures of normal and cancer endometrial tissues	B[a]P	miR-126$^{\downarrow}$, miR-190a$^{\uparrow}$	MiR-126 increased the expression levels of *EGFL7* gene in normal and malignant endometrial tissues; mir-190a decreased the mRNA levels of *TP53INP1* and *PHLPP1* genes in normal cells	Chanyshev et al. (2019)
BEAS-2B cells and C57BL/6 mice	B[a]P and SO_2	mir-30c-1-3p$^{\downarrow}$	Increase in expression of pro-fibrotic genes and TGFβR2	Wu et al. (2019)
Human trophoblast Swan 71 cells	BPDE	miR-194-3p$^{\uparrow}$	Decrease in viability, migration and invasion ability of cells, inhibited PI3K/AKT/CDC42/PAK1 signaling pathway (involved in the filopodia formation)	Tian et al. (2018)
MCF-7 and MDA-MB-231 cells	B[a]P	let-7a$^{\downarrow}$, miR-21$^{\uparrow}$	Altered expression of inflammation mediators (COX-2, TNF-α, and IL-6) and increased migration and invasive potential of human mammary cancer cells	Malik et al. (2018)
Beas-2B cells and C57BL/6J female mice	B[a]P and BPDE	miR-205$^{\uparrow}$	Reduced expression of tumor suppressor protein PHLPP2 and increased expression of TNFα	Huang et al. (2015)
HepG2 liver cells	B[a]P	miR-181a-1_3p$^{\uparrow}$	Inhibition of a DNA damage response enzyme O6-methylguanine DNA methyltransferase (MGMT)	Caiment et al. (2015)
HeLa cells	B[a]P	miR-25$^{\uparrow}$, miR-15a$^{\uparrow}$, miR-16$^{\uparrow}$, miR-92$^{\uparrow}$, miR-125b$^{\uparrow}$, miR-141$^{\uparrow}$, miR-200a$^{\uparrow}$	Repression of p53-targeting miRNAs	Gordon et al. (2015)
A549 and HepG2 cells	B[a]P and TCDD	miR-203$^{\uparrow}$	Suppression of the AhR expression and its downstream regulated genes (cytochrome P450 1A1, 1A2, and NADPH dehydrogenase 1)	Li et al. (2014)
Human bronchial epithelial cell	B[a]P	miR-34c$^{\downarrow}$	Increased expression of cyclin D and B	Han et al. (2014)
HepG2 cells	B[a]A and B[k]F	miR-181a$^{\uparrow}$, miR- 181b$^{\uparrow}$, miR-181d$^{\uparrow}$	Repression of MAPK phosphatase-5 expression, increased phosphorylation of p38 MAPK, and increased cell migration	Song et al. (2013)
A549, H1299 and MRC-5 cells	BPDE	miR-29a$^{\downarrow}$	Increased expression of Cdc7 kinase and its activating subunit Dbf4 and induction of S-phase cell cycle check point	Barkley and Santocanale (2013)
HepG2 cells	B[k]F	miR-146a$^{\uparrow}$, miR-365$^{\uparrow}$, let-7f$^{\uparrow}$, miR-199b-5p$^{\uparrow}$, and miR-30c-1$^{\uparrow}$	Differential expression of mRNAs involved in genotoxicity and carcinogenicity (DNA damage repair, apoptosis, cancer, VEGF signaling, and Jak-STAT signaling)	Song et al. (2012)
Human bronchial epithelial cells, NSCLC tissues, and peripheral lymphocytes	B[a]P	miR-638$^{\downarrow/\uparrow}$	Increase (70%; $p<0.01$) in the CBMN frequency	Li et al. (2012a)
HepG2 cells	B[a]P	miR-29b$^{\uparrow}$, miR-26a-1$^{\uparrow}$, miR-122$^{\downarrow}$	Differential expression of mRNAs involved in genotoxicity (apoptotic signaling, cell cycle arrest, DNA damage response, and repair)	Lizarraga et al. (2012)
Murine bronchial epithelial cells	B[a]P	miR-320$^{\uparrow}$, miR-494$^{\uparrow}$	Cell cycle arrest at G1/S transition and downregulated expression of CDK6	Duan et al. (2010)

B[a]P benzo(a)pyrene, *B[k]F* benzo[k]fluoranthene, *B[a]A* benzo(a)anthracene, *BPDE* benzo[a]pyrene-7,8-diol-9,10-epoxide, *AhR* aryl hydrocarbon receptor, *HBE* human bronchial epithelial cells, *CBMN* cytokinesis-blocked micronucleus assay, *NSCLC* non-small-cell lung cancer, *CDK6* cell division protein kinase 6, *VEGF* vascular endothelial growth factor, *TGFbR2* transforming growth factor, beta receptor II

Table 3 Animal model-based studies on differential expression of miRNA upon exposure to PAHs

Animals	Pollutant	Affected miRNAs	Cellular/physiological changes	Reference
Chinese rare minnow (*Gobiocypris rarus*)	PHE	miR-17$^{\uparrow}$, miR-18a$^{\uparrow/\downarrow*}$, miR-19a$^{\uparrow}$, miR-19b$^{\uparrow}$, miR-20a$^{\uparrow}$, miR-92b$^{\uparrow}$	Decrease in mitochondrial membrane potential in hepatocytes and increase in liver lesion frequency and hepatocyte apoptosis	Hong et al. (2017)
Female Wistar rats	B[a]P	miR-21$^{\downarrow}$	Increase and subsequent drop in mRNA and protein levels of *Acat1*, *Armcx1*, and *Pten* genes	Chanyshev et al. (2017)
Medaka fish (*Oryzias latipes*)	B[a]P	miR-199a-3p$^{\uparrow}$, miR-27b-5p$^{\uparrow}$, miR-26$^{\uparrow}$, miR-214$^{\uparrow}$, miR-204$^{\downarrow}$	Decreased bone thickness and increase in number of microcracks	Seemann et al. (2017)
Caenorhabditis elegans	B[a]P	miR-1$^{\downarrow}$, miR-50$^{\uparrow}$, miR-51$^{\uparrow}$, miR-796$^{\uparrow}$, miR-797$^{\uparrow}$, miR-84$^{\uparrow}$	The mRNA levels of SKN-1 decreased and that of GCS-1 increased	Wu et al. (2015)
Balb/c mice	B[a]P	mmu-miR-140, 199b, 207, 290, 291a-3p, 291a-5p, 291b-5p, 292-3p, 292-5p, 298, 346, 351, 376b, 433-5p, 434-3p, 464, 483, 489, 503, 542-5p, 546	Presence of B[a]P-DNA adduct in all target and non-target organs. Differential expression of *Tubb5*, *Fos*, *Cdh1*, *Cyp1a1*, *Apc*, *Myc*, *Ctnnb1*, and *Cav* genes among target and non-target organs	Zuo et al. (2014)
Female Swiss albino mice	DMBA	miR-203$^{\downarrow}$	Upregulation of histone deacetylases, DNA methyltransferase, and promoter methylation of miR-203. Upregulation of DICER1 and Ago2 expression at both mRNA and protein levels	Tiwari and Gupta (2014)
Female Wistar rats	B[a]P and MC	*Liver:* miR-21$^{\downarrow}$, miR-221$^{\downarrow}$, miR-222$^{\downarrow}$, miR-429$^{\downarrow}$ *Ovary:* miR-21$^{\uparrow}$, miR-221$^{\uparrow}$, miR-222$^{\uparrow}$, miR-429$^{\uparrow}$	Increase in mRNA levels and protein content of CYP1A1 and CYP2B1 and EROD and PROD activities	Chanyshev et al. (2014)
Muta mouse	DB[ah]A	miR-34a$^{\uparrow}$	Increase in liver DNA adducts levels and lacZ mutant frequency. Altered expression of genes implicated in cancer and essential vital functions like circadian rhythm, glucose metabolism, lipid metabolism, immune response, cell cycle and apoptosis	Malik et al. (2013)
Adult male B6C3F1 mice	B[a]P	miR-150$^{\downarrow}$, miR-142-5p$^{\downarrow}$, miR-122$^{\downarrow}$, miR-34c$^{\uparrow}$, miR-34b-5p$^{\uparrow}$, miR-29b$^{\uparrow}$	Increase in B[a]P-DNA adducts in lung and liver tissues, downregulation of B and T cell receptor signaling cascade, and changes in pulmonary and hepatic gene expression	Halappanavar et al. (2011)

* In primary hepatocytes

PHE phenanthrene, *DB[a,h]A* dibenz[a,h]anthracene, *BPDE* benzo[a]pyrene-7,8-diol-9,10-epoxide, *MC* 3-methylcholanthrene, *DMBA* 7,12-Dimethylbenz(α)anthracene, *EGFL7* epidermal growth factor-like domain 7, *TP53INP1* tumor protein p53-inducible nuclear protein 1, *PHLPP1* PH domain and leucine rich repeat protein phosphatase-1, *MNU* N-methyl-N-nitrosourea, *GCS-1* gamma glutamyl cysteine synthetase-1

190a, miR-221, and miR-222 in primary cell cultures in normal and malignant endometrial tissues.

Changes in the level of expression were observed only for miR-126 and miR-190a upon B[a]P treatment. A reduction in the expression level of miR-126 with an increase in the expression level of EGFL7 in normal and malignant endometrial tissues was observed. EGFL7 is involved in cell proliferation and inflammation, promotes tumor growth and angiogenesis, and acts as a target for glioma therapy (Li et al. 2015; Wu et al. 2009). mir-190a is a negative regulator of TP53INP1 and PHLPP1 in normal cells resulting in enhanced cell proliferation and decreased apoptosis. TP53INP1 plays a vital role in cell cycle arrest and activates apoptosis (Tomasini et al. 2005). Moreover, the gene PHLPP1 encodes a phosphatase which is responsible for blocking the signaling pathway PI3K/AKT/mTOR by inactivating AKT2 (Gao et al. 2005). Wu et al. (2019) reported that co-exposure of PAHs and sulfur dioxide (SO_2) causes adverse effects on pulmonary pro-fibrosis via decreasing the mir-30c-1-3p expression level which in turn increases the expression levels of proteins of pro-fibrotic genes and TGFbR2, which plays a significant role in pulmonary fibrosis. In another study, benzo[a]pyrene-7, 8-diol-9, and 10-epoxide (BPDE) exposure in human trophoblast cell line SWAN-71 has been shown to result in upregulation of miR-194-3p and downregulation of the PI3K/AKT/CDC42/PAK1 pathway and inhibiting the filopodia formation. The

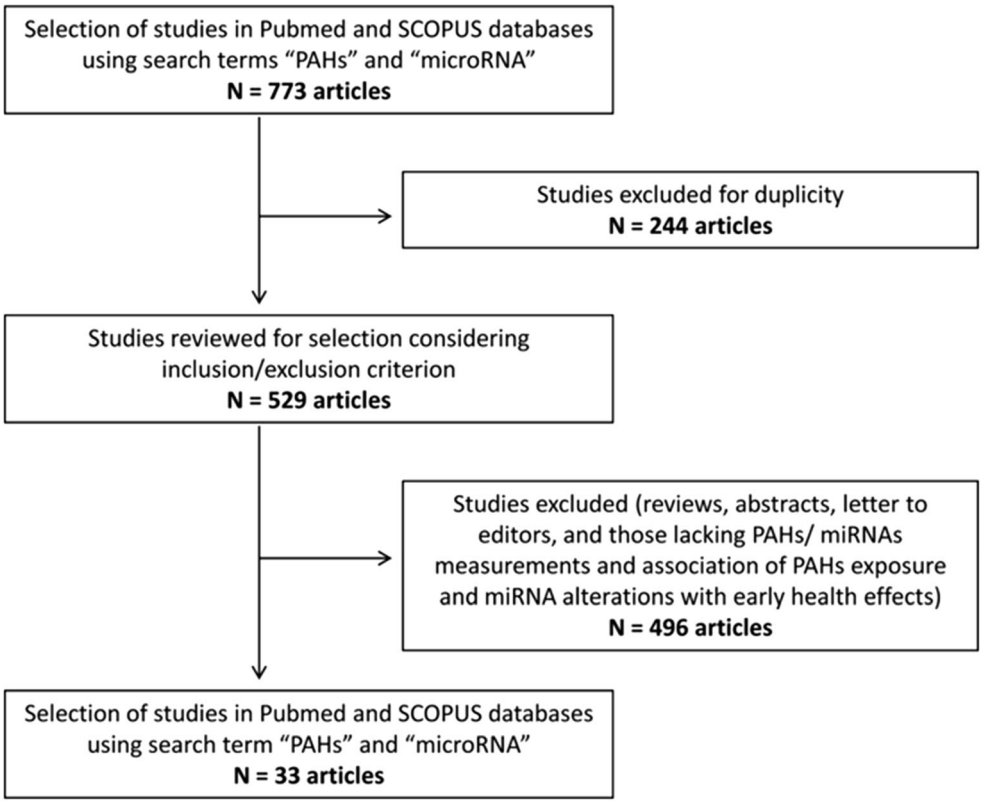

Fig. 4 An overview of methodology adopted for selection of research articles for inclusion in the review.

role of miR-194-3p in BPDE-inhibited filopodia formation and cell migration was further confirmed through knockdown assay (Tian et al. 2018). B[a]P stimulates pathways through tumor necrosis factor-alpha (TNF-α) and NFkappaB (NFκB) resulting in upregulation of IL-6 and dysregulation of some miRNAs (let7a, miR21, and miR29b) which is linked with inflammation microenvironment that accelerates invasion and migration of mammary cancer cells (Malik et al. 2018). Exposure to B[a]P and/or BPDE results in reduced expression levels of PHLPP2 (pleckstrin homology domain leucine-rich repeat protein phosphatase 2), a phosphate-controlling enzyme that catalyzes the dephosphorylation of a conserved regulatory motif on the three AGC kinase family members, AKT, PKC, and S6K1, to inhibit cellular proliferation and induce apoptosis and upregulated levels of miR-205 in mouse lung tissues and human lung epithelial cells. The levels of TNFα—a pro-inflammatory pleiotropic cytokine—were increased in response to the elevated levels of miR-205 in both the exposed mouse lung tissues and human lung epithelial cells (Huang et al. 2015). Another study reported that exposure to B[a]P results in overexpression of miR-181a-1 3p in the human HepG2 liver cells which inhibited O6-methylguanine DNA methyltransferase (MGMT), a DNA damage response enzyme. In chronic exposure conditions, the transiently accumulating O6-MeG mutation was predicted to increase liver cancer risk (Caiment et al. 2015). Gordon et al. (2015) have reported the upregulation of expression level of miR-25, miR-15a, miR-16, miR-92, miR-125b, miR-141, and miR-200a resulting in downregulation of p53-targeting miRNAs in multiple myeloma (MM) cells on exposure to B[a]P. p53 is a tumor suppressor protein which regulates the expression of genes that stimulate cell cycle arrest, apoptotic cell death, and cell senescence (Vogelstein et al. 2000). In another study, it has been shown that exposure to B[a]P and 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) induced the expression of miR-203, which selectively binds at the 3′-UTR region of aryl hydrocarbon receptor (AhR) mRNA leading to reduction of AhR expression at both mRNA and protein levels (Li et al. 2014).

Two studies have described the association of B[a]P-induced changes in cell cycle with altered expression of miRNA in human bronchial epithelial cells. Han et al. (2014) studied changes in p53 function and its target miRNAs in B[a]P-induced transformation of bronchial epithelial cells. It was found that prolonged exposure to B[a]P is associated with accumulation of mutant p53, which caused downregulation of wild-type p53—regulated by miR-34c involved in regulating cell cycle and G2/M arrest via cyclin D and B. The second study by Duan et al. (2010) reported time-dependent increase in the expression level of miR-320 and

miR-494 and downregulation of cyclin-dependent kinase 6 (CDK6) involved in cell cycle arrest at G1/S transition in murine bronchial epithelial cells treated with B[a]P. Interestingly, inhibiting the expression level of miR-320 and miR-494 in treated cells was found to relieve G1 arrest with an increase in CDK6 expression level, suggesting the role of these miRNAs in regulating cell cycle progression through CDK6 whose levels are known to regulate G1/S cell cycle transition. Upregulation of hepatic microRNA-181 family members (miR-181a, miR-181b, and miR-181d) after exposure to benzo[a]anthracene and benzo[k]fluoranthene has been shown to promote cancer cell migration in human liver cells by suppressing MAPK phosphatase-5, which deactivates mitogen-activated protein kinases (MAPKs), thus causing increased phosphorylation of p38 MAPK which is involved in cellular differentiation and chemotactic cell migration (Song et al. 2013). Similarly, exposure to benzo[k]fluoranthene has been found to be associated with alteration of miRNA-mRNA networks in cellular pathways such as DNA damage repair, apoptosis, cancer, VEGF signaling, and Jak-STAT signaling mediated by upregulation of miR-146a, miR-365, let-7f, miR-199b-5p, and miR-30c-1 (Song et al. 2012).

Barkley and Santocanale (2013) have shown that the human lung cancer cells exposed to cigarette smoke {benzo[a]pyrene dihydrodiol epoxide (BPED) source} show BPED-induced DNA damage via increased expression levels of Cdc7, a key enzyme of cellular DNA damage response, which is mediated by downregulation of miR-29a, leading to induction of S-phase cell cycle checkpoint. miR-29a binds to the 3′-UTR region of Cdc7, overexpression of miR-29a results in inefficient checkpoint signaling, generation of elevated levels of double-strand breaks (DSBs), and decreased viability of human lung cancer cells by completely blocking DNA synthesis through phosphorylation of H2AX (gH2AX) and ATM/Chk2 activation. Li et al. (2012a) reported that B[a]P exposure causes differential expression of miR-638. Based on the state of cell malignancy, in PAH exposed workers, the miR-638 was downregulated in B[a]P-transformed cells and human lung cancers cells but upregulated in the immortalized human bronchial epithelial cells and peripheral lymphocytes. The expression level of miR-638 was upregulated resulting in inhibition of the BRCA1, a key protein involved in DNA damage repair by binding to its coding sequence region, resulting in the aggravation of DNA damage which further leads to B[a]P-induced carcinogenesis. HepG2 cells post 6 to 48 h of exposure to B[a]P showed significant alterations in the apoptosis/DNA damage network, DNA repair network, and cell cycle networks mediated by differentially expressed miRNA-29b, miRNA-26a-1, and miRNA-122 (fold change >1.5, $p<0.1$) (Lizarraga et al. 2012). In vitro (cell-based) studies on differential expression of miRNA upon chemical exposure to PAHs have been summarized in Table 2.

PAH-responsive miRNA signatures in animal models (in vivo studies)

Studying the effects of exposure to varying concentration of PAHs at the whole organism level under controlled conditions is facilitated by animal models which can be exposed to various PAH pollutants. A few studies based on animal models of human diseases that have sought to study the systemic effect of PAH exposure and the role of miRNAs in the etiology of various diseases are summarized in Table 3. In one such study, Hong et al. (2017) reported increased liver lesion frequency, hepatocyte apoptosis, and enzyme activity of caspase 9 and caspase 3 and decrease in mitochondrial membrane potential in hepatocytes in Chinese rare minnows fish exposed to 9–510 μg/L phenanthrene (a PAH species) for 30 days. These changes accompany an increase in the expression level of miR-17/92 cluster members and a decrease in miR-18a levels. The DGCR8, Drosha, Dicer, and hnRNP A1 were the potential mRNAs that were regulated by miR-18a levels. Chanyshev et al. (2014) reported that miR-21, 221, 222, and 429 were post-transcriptional regulators of rat cytochrome P450 CYP1A and CYP2B. Decrease in miR-21, 221, 222, and 429 expression levels in the liver of B[a]P treated female rats, while an increase in CYP1A1 and CYP2B1 expression levels, 7-ethoxyresorufin (EROD), and 7-pentoxyresorufin (PROD) activities was found. However, an increase in the level of expression of these miRNAs, as well as CYP1A1 and CYP2B1, was reported in the ovaries of B[a]P-treated female rats. Moreover, B[a]P exposure in female rats was found to result in a reduction of the miR-21 expression level with an increase in the expression of *Acat1*, *Armcx1*, and *Pten* genes (play a key role in oncogenesis) in the liver (Chanyshev et al. 2017). Seemann et al. (2017) reported that even the third generation of medaka (*Oryzias latipes*) larvae could not be recovered from the B[a]P-induced impairment of bone metabolism that persisted trans-generationally from ancestors which were exposed to B[a]P. The authors reported involvement of five pairs of osteogenic mRNA/miRNA (Col2a1b/miR-26, Osx/miR-214, Runx2/miR-204, APC/miR-27b-5p, Sox9b/miR-199a-3p) in the abnormal bone thinning observed in F3 medaka. Antagonistic expression of (i) $Osx^{\downarrow}$/$miR\text{-}214^{\uparrow}$ and $Col2a1b^{\downarrow}$/$miR\text{-}29b^{\uparrow}$ leads to reduce osteoblast maturation and activity, (ii) $Runx2^{\uparrow}$/$miR\text{-}204^{\downarrow}$ results in increased osteoblast differentiation, and (iii) $Sox9b^{\downarrow}$/$miR\text{-}199a\text{-}3p^{\uparrow}$ and $APC^{\downarrow}$/$miR\text{-}27b^{\uparrow}$ results in a reduction of osteoblast differentiation repression (where $^{\uparrow}$ and $^{\downarrow}$ represent upregulation and downregulation, respectively).

Wu et al. (2015) showed that exposure of B[a]P in *C. elegans* causes a decrease in expression levels (mRNAs) of SKiNhead-1 (SKN-1) (a key regulator of oxidative stress) and an increase in expression levels of miR-84 and miR-51, indicating a possibility of SKN-1 regulation by miR-84. Furthermore, the increase of gamma-glutamine cysteine

synthase heavy chain (GCS-1) (modulate glutathione homeostasis) and reduction in miR-1, miR-50, miR-796, and miR-797 suggests a possibility of GCS-1 regulation by miR-1. Zuo et al. (2014) showed that a group of male and female mice receiving doses of B[a]P showed a dose-dependent formation of B[a]P-DNA adducts which do not vary vastly in target organs (spleen, lung, and forestomach) or non-target organs (colon, liver, and glandular stomach). However, analysis expression patterns of 21 miRNAs (miR-140, 199b, 207, 290, 291a-3p, 291a-5p, 291b-5p, 292-3p, 292-5p, 298, 346, 351, 376b, 433-5p, 434-3p, 464, 483, 489, 503, 542-5p, 546) and gene expression profiles were found to indicate tissue-specific responses to B[a]P exposure; genes Tubb5, Fos, Cdh1, Cyp1a1, Apc, Myc, Ctnnb1, and Cav exhibited differential expression in target and non-target organs. Despite the linear relationship between exposure doses, and the levels of DNA-PAHs adduct and tumor incidences in various organs, it is difficult to identify target organs for PAH-associated carcinogenicity based merely on and persistence of DNA damage in these organs. Another study on female Swiss mice exposed to dimethylbenz[a]anthracene (DMBA) reported DNA methylation-mediated silencing of tumor suppressor miRNA, miR-203, leading to skin tumor development. DNA methyltransferase, histone deacetylases (HDAC), promoter methylation, B-lymphoma Mo-MLV insertion region 1 homolog (BMI1), and the proto-oncogene c-Myc were upregulated with downregulation of miR-203 at 4–16 weeks of exposure. Administration of a combination of compounds nicotinamide butyric acid and calcium glucarate was shown to prevent the tumorigenic alterations by regulating miR-203 levels through epigenetic modulations. Thus, reduced expression of miR-203 results in the induction of target oncogenic pathways, which is an important mechanism of tumorigenesis (Tiwari and Gupta 2014).

Malik et al. (2013) studied the hepatic genotoxicity and toxicogenomic responses to the exposure of dibenz[a,h]anthracene (DB[a,h]A) (6.25, 12.5, 25 mg/kg/day) in transgenic Muta mouse and observed a dose-dependent elevation in both lacZ mutant frequencies and DNA adduct formation in the liver with upregulation of miR-34a. At 3 days of exposure (25 mg/kg/day), the formation of approximately 26 DNA adducts per 10^8 nucleotides and 20 lac Z mutants per 10^5 recovered transgene copies was reported. Further, the exposure also led to perturbation in the miRNA and mRNA expressions related to various biological processes and molecular functions including cell cycle arrest, glucose and lipid metabolism, apoptosis, circadian rhythm, and inflammation and immune response. Halappanavar et al. (2011) studied the miRNA profiles in B6C3F1 mice acutely exposed to B[a]P for 3 days (50 and 300 mg/kg) and reported upregulation of miR-34c, miR-29b, and miR-34b-5p and downregulation of miR-150, miR-122, and miR-142-5p which led to increase in B[a]P-DNA adducts in lung and liver tissues, downregulation of B and T cell receptor signaling cascade, and changes in pulmonary and hepatic gene expression.

PAH-responsive miRNA signatures in population-based studies (epidemiological studies)

PAHs produced from combustion and non-combustion processes are known to impact human health by causing oxidative stress, genetic damage, and heart rate variability (HRV). Particularly the coke oven emissions from iron and steel industries that contain significant amounts of PAHs along with other pollutants is one of the major occupational as well as outdoor environmental sources of PAHs. Epidemiological studies that have been carried out for evaluating the association of PAH exposures with aberrantly expressed miRNAs have been summarized in Table 4. One of the studies (Yang et al. 2020) reported that the spermatogenesis-related miRNAs mediate the effects of PAH exposure on semen quality. Exposure to certain PAHs has been shown to reduce semen quality among adult men possibly through PAH-induced changes in spermatogenesis-related miRNAs. The effects of urinary levels of PAHs on decreased sperm concentration among the exposed group were related to the reduced expression of miRNA34c and miRNA106a in seminal plasma.

Mitochondrial DNA is a highly vulnerable target for exogenous carcinogens, and its copy number is considered as a biomarker of oxidative stress (Kim et al. 2014). miR-210 rs11246190 AA, miR-210 rs7395206 CC, and miR-126 rs2297538 GG have been suggested to be responsible for the decrease in copy number of mitochondrial DNA in the peripheral blood leukocyte in coke oven workers exposed to PAHs (Duan et al. 2020a). Duan et al. (2020b) studied the effect of genetic variations on telomeres and mitochondrial DNA copy numbers by considering 3 miRNAs (associated with tumorigenesis), miR145, miR-30a, and miR-197, in PAH-exposed industrial workers. Telomere plays a role in human aging, and diseases like cancers have been found to be significantly shorter in the PAH-exposed group of coke oven workers, which is influenced by the allelomorph miR-197 rs1889470 GG. In women using wood as a source of fuel, the expression level of two vascular-related miRNAs, miR-155 and miR-126, was significantly higher as compared to unexposed. The levels of miRNAs were linked with urinary 1-OHP concentrations in the plasma of exposed women after being adjusted by traditional risk factors, for instance, blood glucose level, blood pressure, age, and serum lipid profile (Ruiz-Vera et al. 2019).

Table 4 Population-based studies on differential expression of miRNA upon environmental exposure to PAHs

Exposed population	Exposure and effect biomarker levels (reference *vs* exposed)	Affected miRNAs	Effects of exposure	References
Men attending an infertility clinic, China (April–June 2013), *n*=111	ΣOH-PAHs: 19.73 μg/g creatinine	miR-106a$^{\downarrow}$, miR-34c$^{\downarrow}$ (spermatogenesis--related miRNAs)	Reduced miRNA levels correlated with the reduced sperm concentration, sperm count, sperm total motility, and progressive motility (all $p< 0.05$) in men showing a dose-response relationships in their urinary PAHs levels (2-OHFlu and 2-OHPh) and reduced seminal plasma miRNAs	Yang et al. (2020)
Coke oven workers China; age 18–60; *n*= 544 exposed, 238 control	1-OHPYR: 5.50 *vs* 83.80 pg/μg creatinine, CED: 0.07 vs 1.12 mg/m^3 per year (all $p<0.001$), mtDNAcn: 1.03 ± 0.31 *vs* 0.60 ± 0.29	miR-210 miR-126 (lung cancer-related miRNAs)	Peripheral blood leukocyte mitochondrial DNA copy number (mtDNAcn) low in the exposed group than the control group ($t = 18.931$, $P<0.001$). mtDNAcn negatively correlated with the levels of 1-OHPYR and CED ($P < 0.001$)	Duan et al. (2020a)
Coke oven workers, China; age 18–60; *n*= 544 exposed, 238 control	1-OHPYR: 5.50 vs 83.80, 1-OHNAP: 24.74 vs 54.41, 2-OHNAP: 26.79 vs 84.97, 3-OHPHE 2.27 vs 18.20 pg/μg creatinine, CED: 0.07 *vs* 1.12 mg/m^3 per year (all $p<0.001$)	miR-145, miR-30a, miR-197 (lung cancer-related miRNAs)	Peripheral blood leucocyte DNA telomere length significantly shorter in exposed group (0.75; 0.51, 1.08) than the control group (1.05; 0.76, 1.44) ($Z = 7.692$, $P<0.001$). Total cumulative exposure dose, 1-hydroxypyrene, 2-hydroxynaphthalene, and 3-hydroxyphenanthrene negatively correlate with telomere length (r = −0.307, −0.212, −0.110, and −0.251, all $p< 0.001$, res)	Duan et al. (2020b)
Biomass smoke-exposed women, Mexico; age 19–81; *n*=100 exposed, 20 control	1-OHPYR: 0.03 vs 0.55 μmol/mol creatinine ($P < 0.01$)	miR-126$^{\uparrow}$, miR-155$^{\uparrow}$ (vascular related miRNAs)	Plasma levels of miRNA expression were associated with urinary 1-OHP ($P < 0.05$)	Ruiz-Vera et al. (2019)
Coke oven workers, steel plant, China; age 20–60 years; *n* = 122 exposed†, 238 reference†	ΣOH-PAHs: 5.21 vs 7.70×10^{-2} μmol/mmol creatine, BPDE-Alb adducts: 4.01 vs 4.46 ng/ mg albumin (all $p <0.001$), 8-OH-dG: 91.66 vs 117.2 nmol/ mmol creatinine ($p<0.001$)	let-7b-5p$^{\uparrow}$, miR-126-3p$^{\uparrow}$, miR-16-5p$^{\uparrow}$, miR-320b$^{\uparrow}$	Altered expression of miRNAs was associated with increased genetic damage; let-7b-5p associated with 9.10% increase of MN frequency , miR-126-3p with 16.85% increase of tail DNA% and 8.95% increase of MN frequency , miR-16-5p with 12.63% increase of MN frequency , and miR-320b with increased MN frequency (all FDR-adjusted $p < 0.05$)	Deng et al. (2019)
Coke oven workers, steel plant, China; age 20–60 years; *n*= 124 exposed, 241 reference	ΣOH-PAHs: 5.20 vs 7.81×10^{-2} μmoL/mmoL creatinine (all $p < 0.01$)	miR-24-3p$^{\downarrow}$, miR-27a-3p$^{\downarrow}$, miR-142-5p$^{\downarrow}$, and miR-320b$^{\downarrow}$	Altered miRNA expression affected the heart rate variability indices (p interaction < 0.05), and associated negatively with RMSSD and/or SDNN (p trend = 0.006, 0.047, 0.019, 0.011, respectively)	Huang et al. (2016)
PAH-exposed coke oven workers, *n*= 1222	ΣOH-PAHs: 3.77 vs 6.72 vs 13.52 ×10^{-2}, μmol/mmol creatinine HF: 164.48 vs 129.75 vs 141.38 ms^2 among low, medium and high exposure group, respectively (all $p<0.001$)	miR-146a	MiR-146a polymorphism associated with low heart rate variability in workers with mir-146a rs2910164 CC genotype than with GG or GC genotype ($P<0.05$). Number of rs2910164 C allele negatively associate with HRV indices in high PAH exposure group; the negative associations were stronger in workers with rs2910164 CC genotype ($\beta<0$, $P<0.05$)	Deng et al. (2016)
Coke oven workers, steel plant, China; age 20–60 years; *n* =	ΣOH-PAHs: 3.16 vs 21.09 × 10^{-2} μmol/mmol creatine; BPDE–Alb: 3.94 vs 6.33 ng/mg albumin. MN frequency: 2 vs 4 per 1000 cells	miR-24-3p$^{\downarrow}$, miR-27a-3p$^{\downarrow}$, miR-142-5p$^{\downarrow}$,	Differentially expressed miRNAs were associated with higher MN frequency ($p < 0.005$), with strong association in	Deng et al. (2014b)

Table 4 (continued)

Exposed population	Exposure and effect biomarker levels (reference *vs* exposed)	Affected miRNAs	Effects of exposure	References
365††, 20 exposed, 20 reference†		miR-28-5p↓, miR-150-5p↑	those consuming alcohol regularly ($p < 0.015$)	
Coke oven workers, steel plant, China; age 20–60 years; *n*= 124 exposed, 241 reference†	ΣOH-PAHs (×10−2): 5.2 vs 7.81 x10^{-2} μmol/mmol creatine, 8-OH-dG: 91.49 vs 117.57 nmol/ mmol creatinine, (all p<0.001), BPDE-Alb: 4.04 vs 4.67 ng/mg albumin	miR-24-3p↓, miR-27a-3p↓, miR-142-5p↓, miR-28-5p↓, miR-150-5p↑	PAH-associated miRNAs were involved in the increase in levels of oxidative DNA damage (8-OH-dG) and decrease in lipid peroxidation (8-iso-PGF2α) biomarkers, especially in workers with lower PAHs exposure levels, in non-smokers, and in non-drinkers	Deng et al. (2014a)

1-OHNAP 1-hydroxynaphthalene, *2-OHNAP* 2-hydroxynaphthalene, *9-OHFLU* 9-hydroxyfluorene, *2-OHFLU* 2-hydroxyfluorene, *3-OHFLU* 3-hydroxyfluorene, *1-OHPHE* 1-hydroxyphenanthrene, *2-OHPHE* 2-hydroxyphenanthrene, *3-OHPHE* 3-hydroxyphenanthrene, *4-OHPHE* 4-hydroxyphenanthrene, *1-OHPYR* 1-hydroxypyrene, *SDNN* standard deviation of all normal to normal NN intervals in electrocardiography record; *RMSSD* root mean of square of successive differences between adjacent normal NN intervals in electrocardiography record, *BPDE–Alb* benzo[a]pyrene-r-7,t-8,c-10-tetrahydrotetrol-albumin, *CED* cumulative exposure dose, *FDR* false discovery rate, *8-OH-dG* 8-hydroxydeoxyguanosine, *8-iso-PGF2α* 8-iso-prostaglandin-F2α

† The exposed groups in coke oven factory are those working at the top of the coke oven or at the side and bottom of the coke oven, whereas controls are workers who worked in offices or at adjunct workplaces

†† Selected among 391 workers based on their ΣOH-PAHs levels.

PAH exposure might have a clastogenic or aneugenic mode of action resulting in an increased frequency of micronucleated cells. The analysis of micronuclei (MN) frequency in binucleated peripheral blood lymphocytes is one of the desired cytogenetic approaches to measure chromosome breakage and loss (Kirsch-Volders et al. 2014). Two studies have reported increased MN frequency among coke oven workers exposed to PAHs. In the first study, increased MN frequency, DNA percent, and increase in 8-OH-dG and/or decrease in 8-iso-PGF2α were associated with differential expression of multiple miRNAs including the let-7b-5p, miR-126-3p, miR-16-5p, and miR-320b which are associated with early health damage (Deng et al. 2019). In another study, Deng et al. (2014b) found that differential expression of the miR-24-3p, miR-27a-3p, miR-142-5p, miR-28-5p, and miR-150-5p is associated with increased MN frequency. The lower level of expression of these miRNAs was associated with urinary 4-hydroxyphenanthrene and/or plasma BPDE-albumin adducts. A higher level of expression of miR-150-5p was linked with urinary 2-hydroxyphenanthrene, 1-hydroxynaphthalene, 2-hydroxynaphthalene, and the sum of monohydroxy-PAHs.

In addition to its well-documented carcinogenic effects on human health, occupational and environmental exposure to PAHs has also been associated with an elevated risk of cardiovascular disease and their risk factors (Holme et al. 2019; Alhamdow et al. 2017; Poursafa et al. 2017). Several studies have reported that a decrease in heart rate variability (HRV) is a marker of altered cardiac autonomic function due to PAH exposure. The effect of PAH-related miRNAs and their polymorphism has been proposed as one of the possible mechanisms linking PAH exposure to altered cardiac autonomic function (Yang et al. 2016; Li et al. 2012c). Deng et al. (2016) described that miR-146a rs2910164 CC genotype is expressed in coke oven workers resulting in lower HRV, indicating that these workers may be more susceptible to cardiac autonomic dysfunction. miR-24-3p, miR-27a-3p, miR-142-5p, and miR-320b in PAH-exposed coke oven workers were negatively associated with HRV indices (Huang et al. 2016). miR-24-3p, miR-27a-3p, miR-142-5p, miR-28-5p, and miR-150-5p were found to be associated with dose-dependent decrease in 8-iso-prostaglandin-F2α (8-iso-PGF2α) and increase in 8-hydroxydeoxyguanosine (8-OH-dG) in varying levels of PAH exposure in coke oven workers (Deng et al. 2014a).

Differentially expressed miRNAs common among the cell-based, animal models and population-based studies

In cell-based, animal models and population-based studies, a total of 11 miRNAs were found differentially expressed in more than one study of a particular group (cell-based or in vivo or epidemiological, as the case may be). Out of the 11 differentially expressed miRNAs, 7 miRNAs were found each in two or more population-based studies (miR-126, miR-142-5p, miR-150-5p, miR-24-3p, miR-27a-3p, miR-28-5p, and miR-320b), 2 miRNAs were found each in more than one animal model studies (miR-291a and miR-292), and 2 miRNAs were found each two or more independent cell-based studies (miR-181a and miR-30c-1). The common differentially expressed miRNAs in the cell-based and animal model studies belong to the miRNA family miR-122, miR-

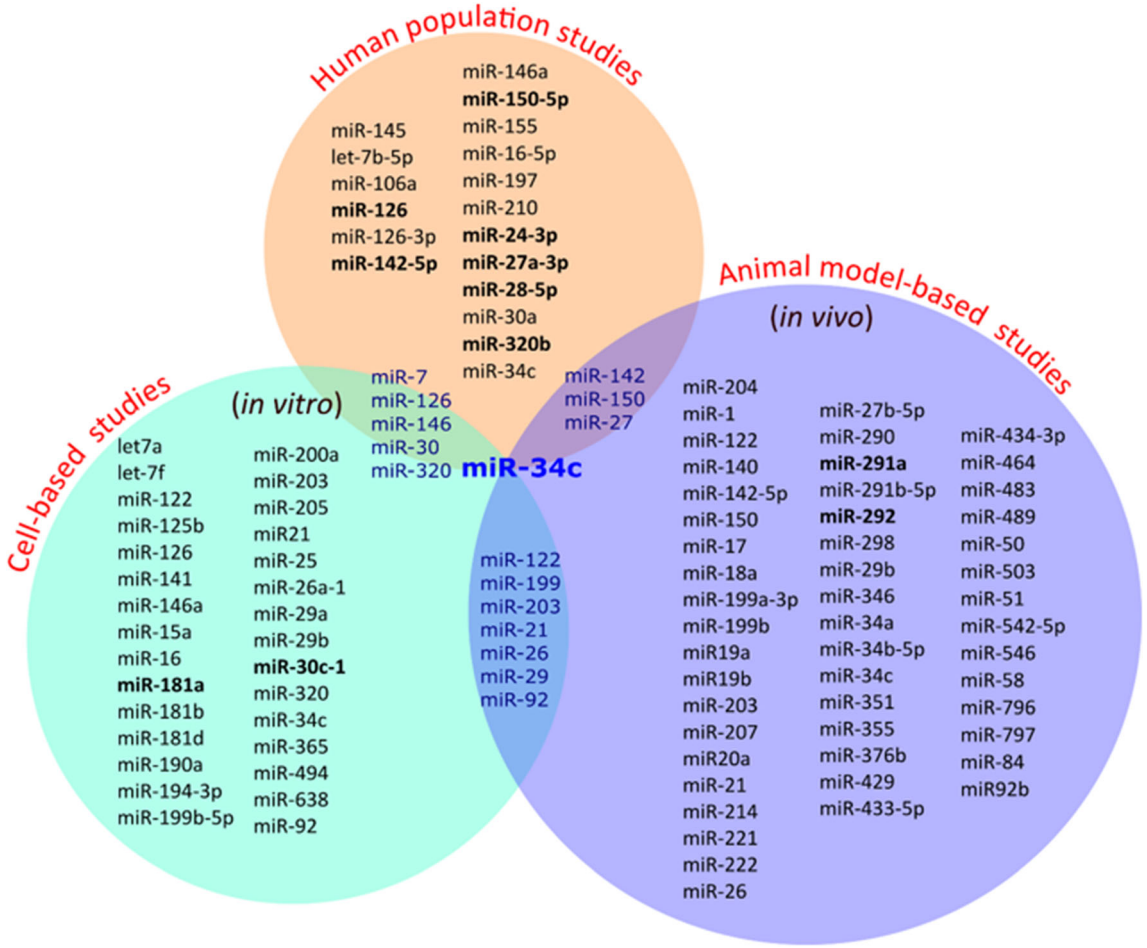

Fig. 5 Venn diagram depicting dysregulated miRNAs associated with PAH exposure as found in the cells (in vitro), animals (in vivo), and human population-based studies. The miRNAs marked in bold are those reported in more than one study in particular group. Common miRNAs among in vivo, in vitro, and human studies are shown in blue color.

199, miR-203, miR-21, miR-26, miR-29, and miR-92. Similarly, let-7, miR-126, miR-146, miR-30, and miR-320 were common between cell-based and population based-studies. Moreover, miR-142, miR-150, and miR-27 were common in animal models and population-based studies. The only miRNA found to be differentially regulated upon PAH exposure among all three groups was miR-34c. Common and distinct PAH-responsive miRNAs from cell-based, animal models and population-based studies are presented in the Venn diagram in Figure 5.

Discussion

The presence of diverse and potentially hazardous chemicals including PAHs in the environment leads to enhanced risk of multiple health issues and diseases. While the impact of environmental exposure to PAHs depends primarily on the route, dose, and duration of exposure, the individual susceptibility derived from interactions between gene and environmental factors contribute equally to determine the observed health effects in the exposed population. Further, the health issues arising from exposure to PAHs cannot be attributed only to direct alteration of expression of protein-coding genes. Several studies have reported that epigenetic effects including DNA methylation, histone modification, and changes in expression of miRNAs may mediate the health effects of PAH exposure. Associating exposome (the lifelong exposures of an individual and their relation to the individual's health) with multi-omics data has emerged as a relatively new discipline in environmental health studies. The growing body of evidence indicates that the expression levels of miRNAs undergo drastic alterations in cells exposed to toxic environmental pollutants. These alterations have been shown to be mediated mainly through the p53-miRNA interaction in response to DNA damage, precursor microRNA-carcinogen adduct formation, and via alterations of Dicer function. Besides, electrophilic metabolites of PAHs have been suggested to alter miRNA levels by forming adducts with miRNA bases (mainly the Guanine) which leads to reduced binding of pre-miRNAs with

the Dicer complex resulting in inhibition of the miRNA maturation process (Izzotti and Pulliero 2014). Altered expression levels of miRNAs can lead to altered levels of the respective target mRNAs as the miRNAs regulate the levels of their target mRNAs via post-transcriptional degradation. Further, miRNAs also crosstalk with other epigenetic changes. For instance, DNA methylation in the miRNA promoter region can modulate miRNA expression levels. On the other hand, miRNAs can regulate DNA methylation via mediating post-transcriptional degradation of transcripts of enzymes involved in DNA methylation.

Variations in the concentration and composition of circulating miRNAs may reveal metabolic states and disease processes. Hence, evaluating the abundance of differentially expressed circulating miRNAs has been beneficial for the identification of new as well as early warning markers of disease and adverse health conditions. Further, recent findings demonstrating intercellular transfer of miRNAs between different cells, for example, between endothelial cells, bronchial epithelial cells, dendritic cells, and mesenchymal stem cells (via extracellular vesicles) in respiratory diseases (Chen et al. 2017), and subsequent alteration in gene expression and functions of target cells indicate that identifying PAH-responsive miRNAs can not only provide exposure and effect-related information, but these miRNAs can also be used as probable therapeutic targets in the future. Also, identifying a panel of dysregulated miRNAs during chemical-induced cell transformation may strengthen our knowledge of the function of miRNAs in disease development and progression.

miRNA alterations at the cellular level (cell-based studies) and/or tissue, organ, or organism level (animal model and human population-based studies) corresponding to early health effects as assessed through changes in physiological and biological parameters have been reported. Cell-based studies are important to understand biological consequences upon exposure to defined concentrations of PAHs in a controlled environment. Cell-based studies on PAH-induced miRNA alterations have delineated a key mechanism of PAH toxicity besides the classical pathways and have also highlighted other mechanisms adopted by cells to maintain cellular homeostasis upon exposure to PAHs. Moving a step further from cell-based studies to animal model studies brings the advantage of understanding disease processes and pharmacokinetics and pharmacodynamics in a more systemic manner. Further, human population-based studies are key to understand the true impact of environmental pollutants on genetically diverse and differentially susceptible group of individuals.

As the circulating population of miRNAs represents only a fraction of tissue-specific miRNAs, both the ability to efficiently recover small quantities of these circulating nucleic acids and the selection of the best source of miRNA among blood, plasma, and other emerging matrices are critical for their successful use in risk assessment. Further, in epidemiological studies, usually the non-invasive/minimally invasive samples collected from apparently healthy individuals are analyzed, which limits, to some extent, our ability to determine the true levels of miRNAs in the source tissues. Hence, the selection of appropriate methods based on factors like sensitivity, specificity, accuracy, and availability to study the expression of miRNAs is equally important. Further, drawing valid and meaningful conclusions from expression analysis data requires careful application of appropriate bioinformatics (miRTarBase, miRanda, MIENTURNET) and statistical techniques. At present, amplification-based techniques (e.g., real-time quantitative reverse transcriptase polymerase chain reaction (qRTPCR)), hybridization-based techniques (microarray chip platforms, e.g., Affymetrix GeneChip® 3.0 and Exiqon mercury LNATM), and sequencing-based techniques (next-generation sequencing, e.g., Illumina Solexa) are used for genome-wide miRNA analysis.

However, it is not yet understood whether PAH exposure induces long-term changes in human miRNA expression or whether these are transient in nature. Moreover, the predictive value of these potential early warning miRNA markers depends on multiple factors such as miRNA-mRNA networks, sources, and tools to collect miRNAs. Multiple miRNAs can bind to a single mRNA, and each of them can regulate mRNA expression differently; therefore, it is difficult to draw conclusions and harness the predictive value of miRNAs solely on the basis of changes in miRNA expression pattern without additional information on the mRNA expression pattern.

Conclusions

In this review, we have presented a critical analysis of the miRNA signatures associated with early health effects of PAH exposure as found in cell-based, animal model-based, and population-based studies. We hope that the findings of this review would aid in enhancing the understanding of the potential of circulating miRNAs as biomarkers of environmental exposure of PAHs and suggest promising future research directions. Based on the findings discussed in the present article as well as elsewhere, further comprehensive analyses of the miRNA-mRNA interaction induced by environmental exposure to PAHs should be carried out in order to further evaluate the potential of miRNAs as effect biomarkers of PAH exposure. Future investigations using an integrated approach to understand the changes in miRNA expression pattern along with the concurrent mRNAs' expression pattern in response to environmental exposure to PAHs would help in generating a more comprehensive picture of crosstalk between PAH exposure and miRNA-mRNA networks and would help in selection of a few miRNA candidates which can reliably function as early warning effect biomarkers of PAH exposure.

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Declarations

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