MicroRNAs as Potential Signatures of Environmental Exposure or Effect: A Systematic Review

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BACKGROUND: The exposome encompasses all life-course environmental exposures from the prenatal period onward that influence health. MicroRNAs (miRNAs) are interesting entities within this concept as markers and causation of disease. MicroRNAs are short oligonucleotide sequences that can interact with several mRNA targets.

OBJECTIVES: We reviewed the current state of the field on the potential of using miRNAs as biomarkers for environmental exposure. We investigated miRNA signatures in response to all types of environmental exposure to which a human can be exposed, including cigarette smoke, air pollution, nanoparticles, and diverse chemicals; and we examined the health conditions for which the identified miRNAs have been reported (i.e., cardiovascular disease, cancer, and diabetes).

METHODS: We searched the PubMed and ScienceDirect databases to identify relevant studies.

RESULTS: For all exposures incorporated in this review, 27 miRNAs were differentially expressed in at least two independent studies. miRNAs that had expression alterations associated with smoking observed in multiple studies are miR-21, miR-34b, miR-125b, miR-146a, miR-223, and miR-340; and those miRNAs that were observed in multiple air pollution studies are miR-9, miR-10b, miR-21, miR-128, miR-143, miR-155, miR-222, miR-223, and miR-338. We found little overlap among in vitro, in vivo, and human studies between miRNAs and exposure. Here, we report on disease associations for those miRNAs identified in multiple studies on exposure.

CONCLUSIONS: miRNA changes may be sensitive indicators of the effects of acute and chronic environmental exposure. Therefore, miRNAs are valuable novel biomarkers for exposure. Further studies should elucidate the role of the mediation effect of miRNA between exposures and effect through all stages of life to provide a more accurate assessment of the consequences of miRNA changes.

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Introduction

Most common diseases result from the combined effect of genes and environmental factors and the interactions between them. Epigenetic effects and non-coding gene products have gained research focus over the last two decades because protein-coding genes cannot account for all observed genomic effects. Here we focus on microRNAs (miRNAs) as key regulators of development, growth, differentiation, and those miRNAs that were observed in multiple air pollution studies are miR-21, miR-10a, and miR-10b. Distinct “hairpin loci that give rise to identical mature miRNAs have numbered suffixes” (e.g., mir-281-1, mir-281-2). The mature sequences are designated “mir.”

miRNA characteristics. miRNA-mediated gene silencing is accomplished by base pairing of the 5′ region of miRNAs with the target mRNA sequence, leading to translational repression and/or mRNA degradation (Ambros 2004). miRNAs have been paradoxically shown to up-regulate gene expression by enhancing translation under specific conditions (Vasudevan et al. 2007). The effect of miRNA expression on gene expression is not linear, as multiple miRNAs may target the same mRNA, and the majority of miRNAs contain multiple binding sites for miRNAs, generating a highly complex regulatory network system (Saetrom et al. 2007). For details on miRNA synthesis, biogenesis, miRNA mechanism of action, see Figure 1 and reviews by Djuricovic et al. (2011) and Murchison and Hannon (2004).

miRNA nomenclature. miRNAs are named using the “miR” prefix and a unique identifying number (e.g., miR-1, miR-2). The identifying numbers are assigned sequentially, with identical miRNAs having the same number, regardless of organism. Paralogous sequences whose mature miRNAs differ at only one or two positions are given lettered suffixes: for example, miR-10a and miR-10b.

miRNA analysis techniques suitable for large epidemiological studies. In recent years, miRNA expression changes following exposure to environmental toxicants, even before disease onset, have gained researchers’ interest. The measure of miRNAs in large epidemiological studies needs to be high throughput and sensitive enough to detect small changes in healthy subjects. At the same time, techniques need to be affordable in order to be conducted in large population studies. Moreover, given the complexity of phenomena induced by exposure but not fully explained by an effect on a single transcript, current research is going toward genome-wide techniques. Another challenge is tissue specificity of miRNAs: The availability of only noninvasive samples in epidemiological studies conducted on healthy populations limits our capability to

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investigate target tissues and opens important questions on the meaning of those markers in surrogate tissues. In epidemiological research, free and exosomal miRNAs in body fluids are interesting study objects because of their potential to serve as a proxy for tissue-specific miRNAs. A limitation of this approach is that these miRNAs differ between different body fluids, and their function is not clear. Although miRNAs hold promise as exposure biomarkers, recent studies have been primarily disease focused [reviewed by Etheridge et al. (2011)].

Genome-wide miRNA analysis can be achieved by amplification-based [real-time quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR)], hybridization-based (microarrays), and sequencing-based [next-generation sequencing (NGS)] technologies. Method selection depends on the type of sample to be analyzed and the RNA preparation protocol used. qRT-PCR is considered the gold standard because of its sensitivity, specificity, accuracy, and simple protocols. qRT-PCR can evaluate candidate miRNA expression or array plates that include a large number of miRNAs in one reaction, to OpenArray™ (Applied Biosystems, Life Technologies), which allows the simultaneous amplification of a very large panel of miRNAs using nanoscale volumes. In a recent review, Prokopec et al. (2013) compared qRT-PCR to different array-based platforms used to study miRNAs/miRNAs.

Several miRNA microarray chip platforms that are commercially available [e.g., Affymetrix GeneChip™ 3.0 miRNA array (Affymetrix Inc.), Agilent Human miRNA Microarray system (Agilent Technologies), Exiqon miRCURY LNA™ microarray (Exiqon Inc.)] differ in probe design and detection stringency. The limitation of this microarray chip method is the availability and stringency of probes on the chip platform that pair with miRNAs of interest. Microarrays have the advantage of being easily correlated to miRNA expression data, thus providing functional information. Furthermore, unlike other current miRNA analysis techniques, microarrays allow fast analysis of miRNAs without an arbitrary preselection step. However, the large amount of data produced can generate false-positive results, and the time-consuming step of validation by qRT-PCR is almost necessary.

NGS strategies based on deep sequencing overcome some of the technical drawbacks of probe-based methodologies, especially the ability to detect only previously known sequences (Schulte et al. 2010). As miRNAs are sequenced directly, information about sequence variations or posttranscriptional RNA editing becomes available for further analysis. The newly developed Nanostring nCounter 27 (Nanostring Technologies Inc.) uses two sequence-specific capture probes to allow for discrimination between similar variants of a single miRNA. NGS technologies [e.g., Illumina/Solexa (Illumina Inc.), GA Roche/454 GS FLX Titanium (Roche Diagnostics Corp.), and ABI/SOLID (Applied Biosystems)] allow complete “miRnomes” to be sequenced and allow for the discovery of novel miRNAs and isoforms. Another benefit of NGS technology is the ability to detect only previously known miRNAs without an arbitrary pre selection protocols. qRT-PCR is almost necessary.

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Figure 1. Overview of miRNA biogenesis. The canonical maturation of a miRNA includes the production of the primary miRNA transcript (pri-miRNA) by RNA polymerase II or III (Pol II/III) and cleavage of the pri-miRNA by the microprocessor complex Drosha–DGCR8 (Pasha) in the nucleus. The resulting precursor hairpin, the pre-miRNA, is exported from the nucleus by Exportin-5–Ran-GTP. In the cytoplasm, the RNASae Dicer in complex with the double-stranded RNA-binding protein TRBP cleaves the pre-miRNA hairpin to its mature length. The functional strand of the mature miRNA is loaded together with Argonaute (Ago2) proteins into the RNA-induced silencing complex (RISC), where it guides RISC to silence target miRNAs through mRNA cleavage, translational repression, or deadenylation, whereas the passenger strand (black) is degraded.

Figure 2. Flowchart of included studies.
MicroRNAs as potential signatures of the exposome

is that it can identify precursor and primary miRNAs as well as their mature forms. NGS will likely become the gold standard for miRNA analysis because of its ability to sequence short fragments in a high-throughput mode. The choice between these methods is a key factor in establishing the possibility of success of any epidemiological study. Each method has pros and cons and should be evaluated based on the specific research.

Methods

**Search strategy and selection criteria.** To identify the articles relevant to this topic, we undertook a comprehensive search of the PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and ScienceDirect (http://www.sciencedirect.com/) databases initially using “microRNA” and “environmental exposure” as key terms. We did additional searches in which we replaced “microRNA” with “mir,” “miRNA,” or “epigenetic changes” and we substituted “environmental exposure” with “smoking,” “passive smoking,” “cigarette smoke,” “air pollution,” “nanoparticle exposure,” “bisphenol A,” “endocrine disruptors,” or “chemical exposure” in every possible combination. We also considered review articles as well as references found in our literature search. We excluded articles not written in English. The PubMed search covered 1 January 1980 to 1 June 2014. Articles dealing only with the description of single nucleotide polymorphisms (SNPs) in miRNA genes were disregarded, as were those articles dealing only with the description of miRNAs in nonmammalian species. A flowchart detailing the search strategy is presented in Figure 2. For miRNAs differentially expressed in response to more than one personal or environmental exposure, we researched disease phenotypes correlated with

**Table 1. miRNAs that are responsive to personal or environmental exposure and their roles in human disease.**

| miRNA | Regulated | Exposure | Diseases | Sources |
|-------|-----------|----------|----------|---------|
| Let-7e | Down | TCDD | HCC, lung, pituitary, and breast cancer, GEP tumors | Feitelson and Lee 2007; Qian et al. 2009; Rahman et al. 2009; Sakurai et al. 2012; Takamizawa et al. 2004 |
| Let-7g | Down | BPA, PM | Lung cancer, GEP tumors, breast cancer | Rahman et al. 2009; Sakurai et al. 2012 |
| mir-9 | Up | Aluminum | Hodgkin lymphoma, breast cancer | Leucci et al. 2012; Ma et al. 2010 |
| mir-10b | Down | Formaldehyde, PM | Gastric cancer | Kim K et al. 2011 |
| mir-21 | Down | Smoking | Diabetes type 2 | Zampetaki et al. 2010 |
| mir-26b | Up | DEP, metal-rich PM | Breast cancer, glioblastoma, neo-intimal lesions, cardiac hypertrophy, atherosclerosis | Ji et al. 2007; Raitoharju et al. 2011; van Rookj et al. 2007; Volinia et al. 2006 |
| mir-31 | Down | DEP, BPA, PF0A | Medulloblastoma, T-cell leukemia | Earle et al. 2010; Liu et al. 2011; Perkins et al. 2007 |
| mir-34b | Down | Smoking (2×) | CRC, pancreatic, mammary, ovarian, and renal cell carcinoma | Vogt et al. 2011 |
| mir-92b | Down | Smoking, DDT | Medulloblastoma | Genovesi et al. 2011 |
| mir-122 | Down | Smoking | HCC | Bai et al. 2009 |
| mir-125b | Down | DEP | Breast cancer, head and neck cancer | Nakai et al. 2014; Zhang et al. 2011 |
| mir-135b | Down | DEP | Medulloblastoma, T-cell leukemia | Vogt et al. 2011 |
| mir-142 | Down | Formaldehyde | Heart failure | Voellenkle et al. 2010 |
| mir-143 | Down | Smoking, PM, ozone | Colon cancer | Zhu et al. 2009 |
| mir-146a | Down | BPA, aluminum sulfate (2×) | Postpartum psychosis, type 2 diabetes | Weigelt et al. 2013; Zampetaki et al. 2010 |
| mir-149 | Up | BPA, DDT | Melanoma | Jin et al. 2011 |
| mir-155 | Up | PM | Breast cancer, Hodgkin lymphoma, B-ALL | Chang et al. 2011; Kong et al. 2014; Palma et al. 2014 |
| mir-181a | Down | Formaldehyde | Leukemia, glioma, NSCLC, breast cancer, metabolic syndrome, and CAD | Gao et al. 2010; Hulsmans et al. 2012; Marcucci et al. 2008; Ota et al. 2011; Shi et al. 2008 |
| mir-203 | Down | Smoking, formaldehyde | Myeloma | Wong et al. 2011 |
| mir-205 | Up | Smoking (2×) | Heart failure, lung cancer | Thum et al. 2007; Yamahe et al. 2006 |
| mir-206 | Up | Smoking, RDX | Myocardial infarct, slows ALS progression, myotonic dystrophy | Gambardella et al. 2010; Shan et al. 2009; Williams et al. 2009 |
| mir-222 | Up | Metal-rich PM, BPA | Severe preeclampsia, thyroid carcinoma, prostate cancer, breast cancer | Hu et al. 2009; Miller et al. 2008; Pallante et al. 2006 |
| mir-223 | Down | Smoking | AML | Eycholzer et al. 2010 |
| mir-338-5p | Down | Formaldehyde | Heart failure, atherosclerosis | Greco et al. 2012; Kin et al. 2012 |
| mir-340 | Down | Smoking | NA | NA |
| mir-638 | Up | BPA, DDT, arsenic | Lupus nephritis | Dai et al. 2009 |
| mir-863 | Up | BPA, DDT, arsenic | CTCL, nasopharyngeal carcinoma, burns | Liang et al. 2012; Ralfkiaer et al. 2011; Yi et al. 2012 |

Abbreviations: ACC, acute lymphocytic leukemia; ALS, amyotrophic lateral sclerosis; AML, acute myeloid leukemia; B-ALL, B-cell acute lymphocytic leukemia; BPA, bisphenol A; CAD, coronary artery disease; CRC, colorectal carcinoma; CTCL, cutaneous T-cell lymphoma; DDT, dichlorodiphenyltrichloroethane; DEP, diesel exhaust particles; GEP, gastroenteropancreatic; HCC, hepatocellular carcinoma; NA, not applicable; NSCLC, non-small cell lung carcinoma; PFOA, perfluorooctanoic acid; PM, particulate matter; RDX, hexahydro-1,3,5-trinitro-s-triazine; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin.
them by searching each of these miRNAs on the Human microRNA Disease Database (HMDD; http://202.38.126.151/hmdd/mirna/md/) and the miR2Disease Base (http://www.mir2disease.org/). Results of these searches are presented in Table 1, including the direction of regulation (up or down) of the miRNA and the ensuing phenotype.

Results

Smoking-induced changes in miRNA expression. The most studied environmental factor in relation to epigenetics is smoking; it was among the first factors shown to affect the miRNA machinery in humans (Spira et al. 2004). Results of in vitro studies concerning smoking and miRNAs are summarized in Table 2. Izzotti et al. (2009) analyzed miRNA expression patterns in the lungs of mice exposed to passive cigarette smoke, and they established life-course–related miRNA expression changes by comparing miRNA expression in lungs from unexposed newborn, postweaning, and adult mice. These researchers observed developmental-stage–specific miRNA expression profiles in which miRNAs that were highly expressed in newborns tended to be less expressed in adult mice and vice versa, whereas miRNA expression in postweaning mice was intermediate (Izzotti et al. 2009). Results from in vivo studies concerning smoking and miRNAs are shown in Table 3.

Two studies reported a comparison between miRNA and mRNA whole genome expression patterns for smokers and nonsmokers (Schembri et al. 2009; Takahashi et al. 2013). Takahashi et al. (2013) reported that quitting smoking altered the plasma miRNA profiles to resemble those of nonsmokers. In addition, Let-7c and miR-150 could be of importance in the initiation of smoke-induced decline of lung function, because genes that were associated with lung function impairment in genome-wide association studies have been reported to be significantly enriched in binding sites for these miRNAs, namely STAT3 (Qu et al. 2009) and TNFR-II (D’hulst et al. 2006).

The effect of in utero exposures on health during childhood and later in life is a growing area of research interest with major public health implications (Gluckman et al. 2008). An adaptive response in the fetus to in utero exposures can result in persistent changes into adulthood. miRNA expression levels in placenta can affect health later in life (Maccani et al. 2011). Studies on miRNA expression and human exposure at different stages of life (in utero, adult) are included in Table 4.

Not surprisingly, miRNAs that are frequently observed to be down-regulated in Table 2. In vitro studies on the effects of smoking on differential miRNA expression.

| miRNA  | miR function               | Regulation | Tissue/cell type | Source   |
|--------|-----------------------------|------------|-----------------|----------|
| mir-15a| Tumor suppressor            | Down       | Primary bronchial epithelial cells | Schembri et al. 2009 |
| mir-125b| Targets p53, stress response |            |                 |          |
| mir-199a| Oncogene activation         |            |                 |          |
| mir-218| Tumor suppressor            |            |                 |          |
| mir-31| Apoptosis, tumor suppressor | Up          | Normal and cancer lung cells | Xi et al. 2010 |
| mir-21| Fatty acid synthesis, apoptosis | Up       | Human squamous carcinoma cells | Zhang et al. 2014 |
| mir-452| Targets CDK1                | Down       | Human alveolar macrophages | Graff et al. 2012 |

Table 3. In vivo studies on the effects of smoking on differential miRNA expression.

| miRNA  | miR function               | Regulation | Tissue/cell type | Source   |
|--------|-----------------------------|------------|-----------------|----------|
| mir-34b| p53 effector               | Down       | Mouse lung      | Izzotti et al. 2011 |
| mir-421| Targets SMAD4, polycomb gene CBX7, ATM |            |                 |          |
| mir-450b| No validated targets      |            |                 |          |
| mir-466| No validated targets      |            |                 |          |
| mir-469| Mouse miR not validated   |            |                 |          |
| mir-135b| Inflammation, oxidative stress | Up       | Mouse lung      | Halappanavar et al. 2013 |
| mir-206| Targets SERP1, BDNF, FOX1P | Up          | Rat serum       | Wu et al. 2013 |
| mir-132b| Targets LAG1, FTY72       | Up          | Mouse lung and plasma | Huang et al. 2012 |
| mir-30e| Targets UBC5, UBE21, MUC17 | Down       |                 |          |
| mir-125b| Targets p53, stress response |            |                 |          |
| mir-128| Apoptosis                 |            |                 |          |
| let-7a| Cell proliferation, angiogenesis | Down       | Mouse lung      | Izzotti et al. 2009 |
| let-7b| Cell proliferation, angiogenesis | Down       |                 |          |
| let-7f| Cell proliferation, angiogenesis | Down       |                 |          |
| miR-21| Fatty acid synthesis, apoptosis Up PlasmMV | Badrnya et al. 2014 |
| mir-150| Hematopoiesis            |            |                 |          |
| let-48| Stress response           |            |                 |          |
| let-144| Stress response, cell growth and differentiation | Down       |                 |          |
| miR-125a| Oncogene activation, RDS     | Down       |                 |          |
| miR-140| p53 effector             |            |                 |          |
| miR-192| Oncogene activation       |            |                 |          |
| miR-431| Protein repair, oncogene activation | Down       |                 |          |
| miR-92b| Tumor suppressomiR         | Down       | Mouse serum     | Yuchuan et al. 2014 |
| miR-668| Inflammation              |            |                 |          |
| miR-700| Inflammation              |            |                 |          |
| let-7a| Apoptosis                 |            |                 |          |
| miR-19a| OncomiR                   |            |                 |          |
| miR-142| Immunology                |            |                 |          |
| miR-191| OncomiR                   |            |                 |          |
| miR-350| Unknown                   |            |                 |          |

Abbreviations: oncomiR, miR with oncogenic properties; RDS, reactive oxygen species; suppressomiR, tumor suppressor miR.

Table 4. Human studies on the effects of exposure to smoking on differential miRNA expression.

| miRNA  | miR function               | Regulation | Tissue/cell type | Source   |
|--------|-----------------------------|------------|-----------------|----------|
| miR-16| p53, cell cycle, JAK/STAT signaling | Down       | Placenta        | Maccani et al. 2010 |
| miR-21| Fatty acid synthesis, apoptosis | Down       | Spermatozoa     | Herberth et al. 2013 |
| mir-146a| Inflammation, NFκB mediator | Down       | Spermatozoa     | Marczylo et al. 2012 |
| mir-223| Immunology                |            |                 |          |
| mir-129| Cell cycle regulation, apoptosis | Down       | Spermatozoa     | Marczylo et al. 2012 |
| mir-834| Inflammation              |            |                 |          |
| mir-340| Cell migration and invasion | Down       | Spermatozoa     | Van Pottelberge et al. 2011 |
| mir-365| Targets NKX2.1            |            |                 |          |
| mir-143| Cardiogenesis             |            | Gastric tissue  | Stätnitz et al. 2013 |
| mir-21| Fatty acid biosynthesis, apoptosis | Down       | Gastric tissue  | Stätnitz et al. 2013 |
| mir-454| Inflammation, NFκB mediator | Down       | Induced sputum  | Van Pottelberge et al. 2011 |
| mir-150| Hemopathoieisis         |            |                 |          |
| mir-203| DNA damage response       |            |                 |          |
| mir-340| Cell migration and invasion | Down       |                 |          |
| miR-443| Unknown                   |            |                 |          |
| miR-226| Immunology                |            |                 |          |
| mir-29b| Apoptosis                 |            |                 |          |
| RNU6-2| Reference miR             |            |                 |          |

MV, microvesicles.

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response to smoking have also been identified as down-regulated in lung (Takamizawa et al. 2004), pancreatic (Vogt et al. 2011), and stomach (Rahman et al. 2009) cancer. Development of cardiovascular disease is associated with up-regulation of miR-206 (Shan et al. 2009), and this miRNA has significantly higher expression levels in smokers than in nonsmokers. Furthermore, two miRNAs that are frequently down-regulated in association with cigarette smoke (i.e., miR-21 and miR-146a) have lower expression levels in individuals with type 2 diabetes compared with healthy controls (Zampetaki et al. 2010). Therefore, these miRNAs could support the observation that smoking is an independent risk factor for type 2 diabetes (Cho et al. 2009). Human studies concerning smoking-induced changes of miRNA expression are summarized in Table 4. Figure 3 is a Venn diagram displaying the common and distinct miRNAs from in vitro, in vivo, and human studies on smoking-induced miRNA alterations. miR-125b and miR-21, identified in in vitro and human studies, respectively, were also reported in in vivo studies. Furthermore, several miRNAs were identified in multiple studies, such as miR-34b and miR-146a.

Table 1 summarizes miRNAs with altered expression in response to environmental and/or personal exposures reported in at least two independent studies, along with their known roles in disease etiology. miRNAs observed in association with either environmental or personal exposures are often associated with cancer; in particular, breast and lung cancer and leukemia have been frequently reported (Table 1). Furthermore, many aberrations in the cardiovascular system have been reported, such as hypertension, heart failure, myocardial infarct, and atherosclerosis. Exposures such as air pollution and smoking can cause cardiovascular disease and cancer (Pope et al. 2011); however, the data shown in Table 1 indicate that the listed miRNAs play a causative role in disease etiology, rather than being merely a marker of exposure.

**Air pollution exposure and miRNA expression.** Particulate matter (PM) is a complex mixture of small particles and liquid droplets. Particle pollution is made up of a number of components, including acids, organic chemicals, metals, and soil or dust particles. The size of particles is directly linked to their potential to cause health problems (Brunekreef and Holgate 2002). Although the clinical effects of PM exposure are obvious, the underlying mechanism of disease initiation and progression is less well understood. miRNAs play a pivotal role in maintaining healthy lungs (Nana-Sinkam et al. 2009). Because the lungs are an important target site for PM, we suggest that miRNAs could underlie the observed health effects of PM exposure. In vitro studies on air pollution and miRNAs are summarized in Table 5.

In a cohort study of steel plant workers, Bollati et al. (2010) examined the effect of PM exposure on miRNA expression. Blood samples were collected at the beginning of the working week (‘preexposure’) and at the end of the working week (‘postexposure’). PM mass and metal components measured in the plant were correlated with miRNA expression analyses of blood samples. Urinary 8-hydroxy-2′-deoxyguanosine (8-OH-dG) levels were measured as a readout of oxidative stress. Both miR-222 and miR-21 were significantly increased in post-versus preexposure samples, and only miR-21 expression levels were positively correlated with 8-OH-dG (Bollati et al. 2010). Oxidative stress has been reported to induce miR-21 expression (Cheng et al. 2009). Because the lungs are an important target site for PM, we suggest that miRNAs could underlie the observed health effects of PM exposure. In vitro studies on air pollution and miRNAs are summarized in Table 5.
reported to change gene expression patterns in nasal and lung cells (Kim et al. 2002; Li et al. 2007). The miRNAs reported to be down-regulated in association with formaldehyde exposure have been reported to be involved in the development of diverse tumors (e.g., breast and gastrointestinal cancer, melanoma) as well as heart failure (Table 1). Given the

| miRNA | miRNA function | Regulation | Tissue/cell type | Pollutant | Source |
|-------|----------------|------------|------------------|-----------|--------|
| miR-21 | Fatty acid synthesis, apoptosis | Up | Peripheral blood | 300 μg PM$_{2.5}$/m$^3$ DEP | Yamamoto et al. 2013 |
| miR-30e | Targets KLF3, MUC17 | Up | Spermatozoa | Metal-rich PM | Bollati et al. 2010 |
| miR-10b | Angiogenesis | Up | Spermatozoa | Metal-rich PM | Li et al. 2012a |
| miR-128 | | | | | |

Abbreviations: DEP, diesel exhaust particles; MV, microvesicles; OncomiR, miR with oncogenic properties; PM$_{2.5}$, particulate matter ≤ 2.5 μm in aerodynamic diameter.

Figure 4. Venn diagram displaying common and distinct microRNAs associated with air pollution exposure in *in vitro* and human studies. miRNAs in bold type were identified in more than one study included in this meta-analysis.
capability of formaldehyde to pass deep into lung tissue and enter systemic circulation, the link with cardiovascular disease and cancer has been widely discussed [reviewed by Kim KH et al. (2011)]. Interestingly, mir-181a, one of the miRNAs down-regulated after formaldehyde exposure, was reported to affect the DNA damage response in breast cancer, enabling the identification of aggressive breast tumors based on increased mir-181a expression (Bisso et al. 2013).

Endocrine disruptors. Organochlorine pesticides and plasticizing agents are ubiquitous environmental endocrine-disrupting compounds that impact human health (Rubin 2011). Bisphenol A (BPA) is an industrial plasticizer often used as a coating in food cans and in plastic bottles (Kang et al. 2006). Dichlorodiphenyltrichloroethylene (DDT) is a well-known organochlorine pesticide. Because DDT is very persistent in the environment, accumulates in fatty tissues, and can travel long distances in the upper atmosphere, residues from historical use remain a current threat to human health.

DDT and BPA have been reported to interfere with endogenous estrogen and thyroid hormone, leading to aberrations of the reproductive, immune, and central nervous systems (Chevrier et al. 2013; Liu et al. 2013). DDT (Waliszewski et al. 2001) and BPA (Takahashi and Oishi 2000) cross the placental barrier and can induce in utero effects that could lead to detrimental effects later in life.

Soto et al. (2013) reported that prenatal exposure to BPA can alter mammary development and lead to breast cancer in humans. From a clinical perspective, it is interesting that decreased expression of let-7f has been associated with increased breast cancer risk (Sakurai et al. 2012), and treatment of MCF-7 breast cancer cells with BPA resulted in reduced let-7f expression (Tilghman et al. 2012). Furthermore, mir-146a has been proposed to induce an Alzheimer’s disease pathway (Jiang et al. 2013) and is up-regulated after BPA exposure (Table 1). Therefore, the neurodegenerative consequences of BPA exposure could at least partially be attributed to mir-146a. In vitro studies could provide researchers with interesting miRNAs that have potential to be used as biomarkers for chemical exposure.

Polychlorinated biphenyls (PCBs) were widely used organic chemicals until their production was banned because of environmental concerns (Porta and Zumeta 2002). PCBs are stable compounds that bioaccumulate in fatty tissues (Steele et al. 1986); they have been reported to cause systemic changes in gene expression (Ceccatidli et al. 2006), suggesting that miRNA regulation could be involved in this process. Tsukimori

### Table 7. Studies on nanoparticle-induced changes in miRNA expression.

| miRNA | miR function | Regulation | Pollutant Source |
|-------|--------------|------------|------------------|
| mir-21 | Fatty acid synthesis, apoptosis | Up | 0.268 or 0.162 mg carbon black NP | Bourdon et al. 2012 |
| mir-135b | Inflammation, oxidative stress | Up | 70 nm silica NP | Nagano et al. 2013 |
| mir-146 | Inflammation, NFκβ mediator | Up | 100 nm gold NP | Balansky et al. 2013 |
| mir-122 | Stress response | Up | | |
| mir-192 | Oncogene activation | Up | | |
| Let-7a | Cell proliferation, angiogenesis | Up | | |
| mir-183 | OncomiR | Up | | |

### Table 8. In vitro studies on chemically induced changes in miRNA expression.

| miRNA | miR function | Regulation | Tissue/cell type | Chemical | Source |
|-------|--------------|------------|-----------------|----------|--------|
| let-7g | Cell proliferation, angiogenesis | Down | MCF-7 cells | BPA | Tilghman et al. 2012 |
| let-7f | Cell proliferation, angiogenesis | Down | MCF-7 cells | DDT | Tilghman et al. 2012 |
| mir-21 | Fatty acid biosynthesis, apoptosis | Up | Jurkat T cell line | Arsenic | Sturchio et al. 2014 |
| mir-26b | Wnt, p53, autophagy, TGF-β | Up | Jurkat T cell line | Arsenic | Sturchio et al. 2014 |
| mir-342-3p | Tumor suppressomIR | Down | MCF-7 cells | BPA, DDT | Tilghman et al. 2012 |
| mir-15b | Tumor suppressor targeting BCL2 | Down | MCF-7 cells | BPA, DDT | Tilghman et al. 2012 |
| mir-222 | Cell cycle regulation | Up | MCF-7 cells | BPA, DDT | Tilghman et al. 2012 |
| mir-638 | No known function | Up | MCF-7 cells | DDT | Tilghman et al. 2012 |
| mir-863 | Immunology, oxidative stress | Down | MCF-7 cells | DDT | Tilghman et al. 2012 |
| mir-1919 | No known function | Down | MCF-7 cells | DDT | Tilghman et al. 2012 |
| mir-27b | Angiogenesis | Down | MCF-7 cells | DDT | Tilghman et al. 2012 |
| mir-92b | Tumor suppressomIR | Down | MCF-7 cells | DDT | Tilghman et al. 2012 |
| mir-1308 | No known function | Up | Human placental cell lines | Arsenic | Avisar-Whiting et al. 2010 |
| mir-146a | Inflammation, NFκβ mediator | Up | Human placental cell lines | Arsenic | Avisar-Whiting et al. 2010 |
| mir-150 | Hematopoiesis | Down | Jurkat T cell line | Arsenic | Sturchio et al. 2014 |
| mir-30d | Autophagy | Up | Jurkat T cell line | Arsenic | Sturchio et al. 2014 |
| mir-142 | Immunology | Up | Jurkat T cell line | Arsenic | Sturchio et al. 2014 |
| mir-181a | Apoptosis, oncomIR | Up | Human bronchiolar epithelial cells | Arsenic | Beazheld et al. 2011 |
| mir-219 | Fatty acid biosynthesis, apoptosis | Up | HUVEC cells | Arsenic | Li et al. 2012 |
| mir-24 | Apoptosis | Up | HUVEC cells | Arsenic | Li et al. 2012 |
| mir-229a | Apoptosis | Up | HUVEC cells | Arsenic | Li et al. 2012 |
| mir-35a | Lipid metabolism | Up | HUVEC cells | Arsenic | Li et al. 2012 |
| mir-198 | Cell proliferation | Up | HUVEC cells | Arsenic | Li et al. 2012 |
| mir-508-5p | Cell invasion and migration | Up | HUVEC cells | Arsenic | Li et al. 2012 |
| mir-1252 | No known function | Up | HUVEC cells | Arsenic | Li et al. 2012 |
| mir-181a | Apoptosis, oncomIR | Up | HUVEC cells | Arsenic | Li et al. 2012 |
| mir-181b | Apoptosis, oncomIR | Up | HUVEC cells | Arsenic | Li et al. 2012 |
| mir-181d | Apoptosis, oncomIR | Up | HUVEC cells | Arsenic | Li et al. 2012 |

Abbreviations: NP, nanoparticles; oncomIR, miR with oncogenic properties.

### Figure 5. Venn diagram displaying common and distinct microRNAs associated with arsenic exposure in in vitro and human studies. miRNAs in bold type were identified in more than one study included in this meta-analysis.
et al. (2008) reported an association between maternal PCB exposure and fetal toxicity, impaired fetal growth, and pregnancy loss.

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) has been reported to adversely affect the immune system in rats (Faith and Luster 1979). In addition, Camacho et al. (2004) reported that TCDD exposure of pregnant mice affected the immune system of fetuses by suppressing T-cell function.

Arsenic. Environmental exposure to arsenic, especially to trivalent inorganic arsenic (As³⁺), is a health concern given the high concentrations present in groundwater across the world (Fendorf et al. 2010). Exposure to arsenic has been associated with increased risk of cancer due to genomic instability (Dulout et al. 1996), and long-term arsenic exposure has been observed to induce peripheral vascular injury (Teng 2008). A Venn diagram showing the common and distinct miRNAs from in vitro and human studies on arsenic-induced miRNA alterations is presented in Figure 5. Only miRNA-21 was associated with arsenic exposure in in vitro model systems and in human studies. Three miRNAs were identified by at least two independent studies on arsenic exposure and miRNA expression, namely, miR-26b, miR-181a, and miR-222.

Aluminum sulfates. Aluminum is the most widely distributed metal in the environment and is extensively used in daily life. Chronic exposure of animals to aluminum is associated with behavioral and neuro-pathological changes (Fulgenzi et al. 2014). Epidemiological studies have shown poor performance in cognitive tests and a higher incidence of cancer due to genomic instability (Dulout et al. 1996), and long-term arsenic exposure has been observed to induce peripheral vascular injury (Teng 2008). A Venn diagram showing the common and distinct miRNAs from in vitro and human studies on arsenic-induced miRNA alterations is presented in Figure 5. Only miRNA-21 was associated with arsenic exposure in in vitro model systems and in human studies. Three miRNAs were identified by at least two independent studies on arsenic exposure and miRNA expression, namely, miR-26b, miR-181a, and miR-222.

Hexahydro-1,3,5-trinitro-s-triazine (RDX). The polynitramine explosive RDX is a heavily used second-generation high explosive, and its use can result in the contamination of soils, sediments, and water (Davis et al. 2004). RDX exposure has been reported to be toxic to the neural and immune systems and to increase tumor incidence in several cancers (Garcia-Reyero et al. 2011; Sweeney et al. 2012).

Diethylstilbestrol (DES). The synthetic estrogen DES was prescribed to pregnant women from the 1940s to the 1960s in order to prevent miscarriages; however, DES was later reported to be responsible for increasing breast cancer in the mothers and gynecologic tumor incidence in their exposed daughters (Greenberg et al. 1984; Mittendorf 1995).

Perfluorooctanoic acid (PFOA). Perfluoroalkyl chemicals (PFCs) are highly stable and widely used in industrialized countries. PFCs are both lipophobic and hydrophobic; thus, after absorption they will bind to proteins in serum and liver rather than accumulate in lipids. PFOA is one of the most commonly used PFCs.

miRNAs are omnipresent in the genome and are important regulators of gene expression in response to intracellular as well as environmental cues. In this review, we examined the response of the miRNA machinery to personal and environmental exposures, including air pollution, cigarette smoking, and chemicals such as endocrine disruptors. miRNAs have been proposed as biomarkers for disease; however, the literature also reveals their potential to be used as biomarkers of environmental exposure.

In different studies on the same environmental pollutant, overall the identified miRNAs showed similar patterns of expression regulation. In studies where smoking-induced changes were investigated, the general observation was a down-regulation of expression. For example, miR-125b was down-regulated in response to cigarette smoke in both primary human bronchial epithelial cells (Schembri et al. 2009) and mouse lung tissue (Izzotti et al. 2009). However, when unique miRNAs had altered expression patterns in response to different sources, the results were inconsistent.
environmental exposures, their direction of regulation could be the same (10/25 miRNAs) or the opposite (15/25 miRNAs; 60%). The different exposures we discussed here have their own unique health effects, so one would not expect them to have the same effect on the miRNA machinery. However, there is sometimes a discrepancy when looking at the same exposure indicator; for example, in response to smoking, miR-21 has been reported to be up-regulated in some studies and down-regulated in others (Table 4). Part of the discrepancy can be explained by the different exposure models that were used.

In general, different in vitro studies show little overlap, potentially because of the complex miRNA–mRNA networks that underlie the observations and the differences in exposure used across studies. In studies of the same environmental pollutant in vitro, in vivo, or in humans, identified miRNAs were quite distinct (Figures 3–5). This can be explained in part by the observation that animal models do not always reflect genomic responses that occur in humans (Seok et al. 2013). Discrepancy between different studies might also stem from differences in exposure duration. For example, in a study in rats, the duration of exposure uniquely influenced expression patterns of the individual miRNAs (Izzotti et al. 2011).

Human epidemiological studies are necessary to observe exposure-related effects on miRNAs. Understanding the exposome requires putting together pieces of a complex puzzle. Epidemiological studies need input from experimental studies to identify good candidate biomarkers, and results from epidemiological studies often need follow-up by experimental studies to investigate mechanisms of action and to study tissue dependency of effects because human studies are most often performed in easily accessible tissues such as blood and saliva as a surrogate for the actual target tissues.

Currently, epidemiological studies on microRNA often involve free or exosomal miRNAs present in saliva or other body fluids. However, it is not clear whether these observed miRNA changes are a true reflection of the body’s response and can really predict health effects. In blood, miRNAs within the exosomes have been shown to overlap with cellular miRNA profiles: Cheng et al. (2014) observed that exosomes derived from blood were enriched for miRNAs and that miRNA profiles between blood cells and the cell-free exosomal fraction showed important overlap.

Because miRNAs can regulate mRNA expression in both a negative manner and a positive manner (Vasudevan et al. 2007) and because many miRNAs can bind the same mRNA (Sactrom et al. 2007), it is difficult to draw conclusions from miRNA studies without information on the concurrent mRNA(s) expression pattern. However, this information is rare in current reports on epidemiological studies of miRNAs. The findings of this review underscore the complex networks that are built by miRNAs and the miRNAs they regulate because one miRNA can influence many mRNAs according to the timing and pattern of expression.

Many of the reviewed studies used large-scale microarray profiling, but follow-up and validation with more quantitative approaches often lags behind. This delay is understandable because of the cost and labor intensity inherent to these techniques; however, it is important to confirm the miRNAs that are responsive to environmental exposures.

Researchers are currently publishing extensive lists of miRNAs that are responsive to environmental exposures and showing their utility as biomarkers of effect. Future research should focus on identifying the molecular mechanism behind miRNA expression changes in response to exposure to determine whether the changes in miRNA expression are merely a symptom of the (patho)physiological processes the organism undergoes after exposure, or whether miRNAs are the drivers responsible for these changes. Izzotti and Pulliero (2014) recently reviewed the putative mechanisms of action behind miRNAs’ response to environmental exposure. However, the effect of the identified miRNAs on putative mRNA targets should also be studied to determine whether the change in miRNA expression has functional consequences and which mRNAs are true miRNA targets under the given circumstances.

At present, little is known about whether environmental exposures induce long-term changes in human miRNA expression or whether these have a transient character. To address this problem, more longitudinal studies should be conducted to examine the long-term effects of exposure. Results from animal studies suggest that miRNA expression changes in response to formaldehyde exposure are transient and revert to normal levels after recovery from exposure (Rager et al. 2014), but Izzotti et al. (2011) reported that miRNA profiles in target organs did not recover 1 week after cessation of long-term cigarette smoke exposure. In a study in humans, Takahashi et al. (2013) observed that miRNA expression profiles of individuals who quit smoking resembled those of nonsmokers.

Follow-up in future generations is necessary to determine the heritability of the miRNA expression changes. It would be very interesting to examine the effect of in utero environmental exposures on development of disease in later life and the role miRNAs play in inducing these health effects. Furthermore, long-term longitudinal studies would allow us to distinguish between cause and effect of miRNA expression and environmental exposure, and would also allow us to estimate the contribution of miRNAs to disease development. Studies have shown that miRNAs can be used as biomarkers of disease as well as biomarkers for environmental exposure and that miRNAs hold great potential to explain disease etiology.

**Table 10. Human studies on chemically induced changes in miRNA expression.**

| miRNA | miR function | Regulation | Tissue/cell type | Chemical | Source |
|-------|--------------|------------|-----------------|----------|--------|
| miR-191 | Oncogenic | Up | Peripheral blood | PCB-189 | Guida et al. 2013 |
| miR-146a | Inflammation, NFκB mediator | Up | Fetal brain cells | Aluminum | Pogue et al. 2009 |
| miR-9 | Neuronal differentiation | Up | Fetal brain cells | Aluminum | Lukiw and Pogue 2007 |
| miR-125b | Targets p53, stress response | Up | Fetal brain cells | Aluminum | Lukiw and Pogue 2007 |
| miR-128 | Apoptosis | Up | Fetal brain cells | Aluminum | Lukiw and Pogue 2007 |
| miR-199a | Uncore gene activation | Up | Serum | PFOA | Wang et al. 2012 |
| miR-21 | Fatty acid biosynthesis, apoptosis | Up | Blood samples | Arsenic | Kong et al. 2012 |
| miR-26b | Wnt, p53, autophagy, TGF-β | Up | Blood samples | Arsenic | Kong et al. 2012 |
| Let-7a | Cell proliferation, angiogenesis | Up | Blood samples | Arsenic | Kong et al. 2012 |
| miR-16 | DNA damage response | Up | Cord blood | Arsenic | Rager et al. 2014 |
| miR-17 | DNA damage response | Up | Cord blood | Arsenic | Rager et al. 2014 |
| miR-20a | Angiogenesis | Up | Cord blood | Arsenic | Rager et al. 2014 |
| miR-20b | Hypoxia | Up | Cord blood | Arsenic | Rager et al. 2014 |
| miR-26b | Wnt, p53, autophagy, TGF-β | Up | Cord blood | Arsenic | Rager et al. 2014 |
| miR-54 | Angiogenesis | Up | Cord blood | Arsenic | Rager et al. 2014 |
| miR-107 | Targets Notch2 | Up | Cord blood | Arsenic | Rager et al. 2014 |
| miR-126 | Angiogenesis | Up | Cord blood | Arsenic | Rager et al. 2014 |
| miR-195 | Tumor suppressor | Up | Cord blood | Arsenic | Rager et al. 2014 |
| miR-454 | Unknown | Up | Cord blood | Arsenic | Rager et al. 2014 |
| miR-24 | Oncogenic | Down | Plasma | PAH | Deng et al. 2014 |
| miR-27a | Apoptosis, Erk | Up | Plasma | PAH | Deng et al. 2014 |
| miR-29 | Apoptosis | Up | Plasma | PAH | Deng et al. 2014 |
| miR-142 | Immunology | Up | Plasma | PAH | Deng et al. 2014 |
| miR-150 | Hematopoiesis | Up | Plasma | PAH | Deng et al. 2014 |

Abbreviations: Oncogenic, miR with oncogenic properties; PAH, polycyclic aromatic hydrocarbon; suppressor, tumor suppressor miR.
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