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ORIGINAL PAPER

MicroRNAs and their role in environmental chemical carcinogenesis

Minghui Li · Xia Huo · Chand Basha Davuljigari · Qingyuan Dai · Xijin Xu

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Abstract MicroRNAs (miRNAs) are a class of small, noncoding RNA species that play crucial roles across many biological processes and in the pathogenesis of major diseases, including cancer. Recent studies suggest that the expression of miRNA is altered by certain environmental chemicals, including metals, organic pollutants, cigarette smoke, pesticides and carcinogenic drugs. In addition, extensive studies have indicated the existence and importance of miRNA in different cancers, suggesting that cancer-related miRNAs could serve as potential markers for chemically induced cancers. The altered expression of miRNA was considered to be a vital pathogenic role in xenobiotic-induced cancer development. However, the significance of miRNA in the etiology of cancer and the exact mechanisms by which environmental factors alter miRNA expression remain relatively unexplored. Hence, understanding the interaction of miRNAs with environmental chemicals will provide important information on mechanisms underlying the pathogenesis of chemically induced cancers, and effectively diagnose and treat human cancers resulting from chronic or acute carcinogen exposure. This study presents the current evidence that the miRNA deregulation induced by various chemical carcinogens, different cancers caused by environmental carcinogens and the potentially related genes in the onset or progression of cancer. For each carcinogen, the specifically expressed miRNA may be considered as the early biomarkers of the cancer process. In this review, we also summarize various target genes of the altered miRNA, oncogenes or anti-oncogenes, and the existing evidence regarding the gene regulation mechanisms of cancer caused by environmentally induced miRNA alteration. The future perspective of miRNA may become attractive targets for the diagnosis and treatment of carcinogen-induced cancer.

Keywords MicroRNAs · Environmental chemicals · Carcinogenesis · Cancer

M. Li · C. B. Davuljigari · X. Xu (✉)
Laboratory of Environmental Medicine and Developmental Toxicology, and Guangdong Provincial Key Laboratory of Infectious Diseases and Molecular Immunopathology, Shantou University Medical College, Shantou 515041, Guangdong, China
e-mail: xuxj@stu.edu.cn

X. Huo · Q. Dai
Laboratory of Environmental Medicine and Developmental Toxicology, Guangdong Key Laboratory of Environmental Pollution and Health, School of Environment, Jinan University, Guangzhou 511486, Guangdong, China

X. Xu
Department of Cell Biology and Genetics, Shantou University Medical College, Shantou 515041, Guangdong, China

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Introduction

Accumulating evidence suggests that exposure to environmental chemicals is associated with human health and increases risks for various diseases. Epidemiological and occupational studies have indicated that certain carcinogenic chemicals, including metals, organic pollutants, cigarette smoke, pesticides and drugs, are a major cause of human cancers (World Cancer Report 2014). In recent years, epidemiological studies have indicated that exposure to certain chemicals is a major cause of human cancer. For instance, exposure to arsenic (As) may be linked to bladder cancer (Polo et al. 2017), bisphenol A may be associated with breast cancer (Murata and Kang 2018). Moreover, cigarette smoking has been associated with cancers of the lung (Bordas et al. 2017), bladder (Li et al. 2017a, b, c, d), voice box (Bruzgielewicz et al. 2017), esophagus and pancreas (Yuan et al. 2017a, b). Ferreccio et al. (2013) reported that people co-exposed to As and secondhand tobacco smoke, or another suspected carcinogen, including asbestos, silica and wood dust, have high risks of lung or bladder cancer. These studies provided important insights concerning the interactions between genes and environmental chemicals, and the significance of these interactions in the development of cancers. Smith et al. (2016) described several key characteristics of known human carcinogens, including chronic inflammation, immunosuppressive, alteration cell proliferation, cell death or nutrient supply, epigenetic alterations, oxidative stress, genotoxicity and alteration DNA repair or genomic instability. However, the underlying mechanism is extremely complex and poorly understood.

Cancer is one of the leading causes of death worldwide and the number of new cases is increasing (Chatterjee et al. 2017). A wealth of data demonstrates that changes in epigenetic are associated with almost every step of tumor development and progression (Mehra and Chauhan 2017). There are several major epigenetic alterations in DNA methylation, histones/chromatin structure, nucleosome positioning and noncoding RNAs. These altered epigenetic and epigenomic consequence may result from the environment chemical exposure (Cavalieri and Spinelli 2017). The epigenetic changes are a driving force in chemically induced cancer and may have significance as biomarkers of carcinogen exposure. However, extensive literature indicated the significance of the effect of chemical carcinogen-induced epigenetic alterations in the cancer development, the precise role of miRNAs in chemical-related carcinogenesis remains uncertain.

MiRNAs are a class of small, noncoding RNA species that play critical roles in a series of biological processes, as well as in the diverse physiologic and pathologic processes of various diseases such as cancer (Cantini et al. 2017). Moreover, the alteration of miRNA may be sensitive indicators of the effects of acute and chronic environmental exposure, and the mediation effect of miRNA between exposure and effect through all stages of life (Vrijens et al. 2015). Evidence is rapidly growing that miRNA regulation of gene expression may be affected by environmental chemicals, including metals, organic pollutants, cigarette smoke, pesticides and carcinogen drugs (Izzotti and Pulliero 2014). MiRNA may be sensitive indicators of pollutant exposure and altered miRNA levels can be proposed as biomarkers of cancer (Yang et al. 2017). Despite extensive research indicated various target genes of the altered miRNA on oncogenes or anti-oncogenes, the responsible mechanisms and the role of miRNA in the etiology of chemically induced cancers remain relatively unexplored. Hence, a better understanding of the pathological role of miRNA in relation to environmental factors may be helpful for elucidating the underlying mechanisms in chemically induced cancers and developing effective strategies to prevent disease. The purpose of this review is to summarize the existing findings on miRNA associated with various chemical carcinogens and those mainly involved in the development of tumors. Here, we also discuss the potential molecular mechanisms for miRNA changes caused by chemical carcinogenic hazards and summarize various target genes of the altered miRNA, oncogenes or anti-oncogenes.

MicroRNAs: biogenesis and mechanisms of function

Biogenesis of MicroRNAs

MiRNAs are noncoding, single-stranded RNA molecules of approximately 19–25 nucleotides in length that are transcribed from DNA. Biogenesis of miRNAs involves a complex protein system and starts with the transcription of a long primary miRNA (pri-

miRNAs) by RNA polymerase II (Khan et al. 2017; Mohr and Mott 2015). Subsequently, pre-miRNAs form a stem-loop structure (hairpins), and these transcripts are processed in the nucleus into 70-nt-long precursor miRNAs (pre-miRNAs) by the RNase III endonuclease activity of Drosha and its cofactor DGCR8 (DiGeorge syndrome critical region 8-dependent). These pre-miRNAs are transported from the nucleus to cytoplasm by exportin-5. Here, pre-miRNAs are further processed by a second ribonuclease, Dicer, into a double-stranded RNA duplex that contains a mature miRNA or guide strand and its complement. The complementary strand is believed to be degraded while the other strand (guide strand) is incorporated into an RNA-induced silencing complex (RISC) which exclusively targets and degrades messenger RNA. The process of producing mature miRNA is regulated by several mechanisms and at different stages of miRNA biogenesis. MiRNAs guide RISC to mRNAs that either destabilize or repress the target mRNA (Lin and Gregory 2015). MiRNAs bind to complementary sequences in the 3′-untranslated region (3′-UTR) of their target mRNAs. This interaction between miRNAs and the 3′-UTR of a protein-coding gene results in miRNA destabilization and is considered to be the mechanism of miRNA-mediated posttranscriptional regulation that generally leads to a reduction in protein synthesis (Fig. 1).

Mechanisms of microRNA function

The primary function of miRNA is to inhibit target gene expression by entering the RISC, where miRNA directly regulates by mRNA cleavage or base-pairing to target mRNA to exert posttranscriptional repression. The key mechanism of posttranscriptional regulation is the interaction of miRNAs with the 3′-UTR of protein-coding genes (Oliveto et al. 2017). Initial studies on worm Caenorhabditis elegans showed that lin-4 and let-7 noncoding RNA regulate protein synthesis by translational repression rather than cleavage and degradation (Reinhart et al. 2000). Other study has also provided overwhelming evidence that miRNA-bound mRNA results in mRNA degradation, destabilization, translational inhibition and direct cleavage (Khan et al. 2017). The mechanism of miRNA-mediated mRNA destabilization includes miRNA-mediated target deadenylation, and miRNA interaction with the 5'-UTR of protein-coding genes. MiRNAs can target the coding sequences and repress the translation of such targeted genes (Fig. 1).

MicroRNA carriers

Until now, miRNA carriers have been described as exosomes, apoptosis bodies, membrane-derived vesicles high-density lipoprotein, and ribonucleoprotein complexes (Xi et al. 2016). Exosomes are secreted by various types of cells, such as epithelial cells, lymphocytes, dendritic cells and neurons. Exosomes and their miRNA content are released into the extracellular compartment on the fusion of endosomes with the plasma membrane (Lachenal et al. 2011). Additionally, microvesicles (microparticles or apoptosis bodies) also are larger lipid-based miRNA carriers. Extracellular vesicles have acted as pivotal mediators of intercellular communication, and tightly linked to tumorigenesis (Banelli et al. 2017). To date, many studies focus on the roles of exosomes in cancer, particularly miRNAs. MiRNAs have recently been detected in serum, plasma, saliva, tears, urine, colostrum, breast milk, bronchial secretions and amniotic fluid (Weber et al. 2010). Currently, the focus has been increased on circulating miRNAs, which have been reported to serve as an effective and noninvasive biomarker for detecting various cancers. However, the investigation of miRNA as biomarkers is still in the preliminary stages.

The role of miRNA in cancers

Evidences have demonstrated that miRNA expression is dysregulated in cancer, and the altered miRNA is involved in cancer initiation and metastasis, and act as either oncogenes or tumor suppressors in cancer. Further studies continue to expand rapidly to investigate the altered miRNAs in all types of human cancers, such as miRNA dysregulation during lung, liver and breast carcinogenesis (Pogribny 2009). Previously, most researches focused on the analysis of miRNA expression in tumors in comparison with normal or adjacent tissues are not sufficient to address conclusively the role of aberrant miRNA in the carcinogenic process. However, increasing evidence indicated that aberrant expression of miRNAs could inhibit tumor suppressor genes or inappropriately activate oncogenes and has been associated with tumor progression, invasiveness and metastasis. More

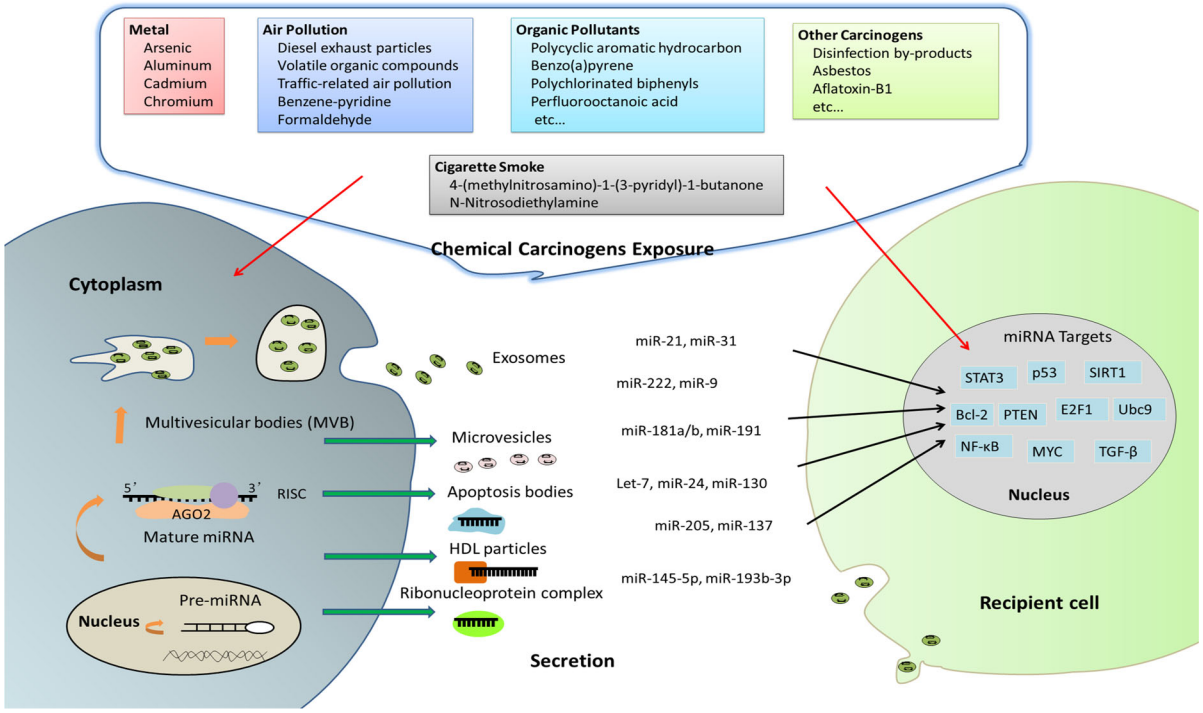

Fig. 1 MicroRNA role in chemical-induced cancer. Metals, air pollution, organic pollutants, cigarette smoke and other chemical carcinogens exposure change the secretion of miRNAs, which are released from cells by being incorporated into the multivesicular bodies (MVBs) and secreted via exosomes. Additionally, miRNAs can be packaged into microvesicles, incorporated into apoptosis bodies, associated with high-density lipoprotein (HDL) particles and ribonucleoprotein complexes. Extracellular vesicles bind to the plasma membrane of a recipient cell, resulting in delivery of the miRNAs and associated with the corresponding mRNA target genes

importantly, circulating tumor cell-derived miRNAs are stable in the serum, plasma and urine of cancer patients may be used as noninvasive molecular biomarkers for early cancer detection, and even miRNA may be an attractive novel target and intervention tool for cancer early therapy. Previous study showed that miR-214 is a determinant of CRC irradiation response and may serve as a potential therapeutic target in CRC treatment (Hu et al. 2018). Given the important roles of miRNA in regulating cellular response to chemical carcinogen exposure, it is likely that miRNAs take part in chemical carcinogen-induced cell malignant transformation and tumorigenic process. This review aims to present an increasing body of evidence and suggests that the dysregulated miRNAs play critical roles in a particular class of chemical carcinogen-induced tumorigenesis.

MicroRNA role in chemical-induced cancers

Chemical carcinogens such as air pollution, cigarette smoke, organic pollutants and metals exposure through air, soil, water and food have been shown to increase the risk of cancer; however, the underlying mechanisms of these chemicals carcinogenesis have not been well understood (Fig. 1). A growing body of evidence has shown that miRNA dysregulation plays an important role in chemical-induced cancers, and the investigation of the role of miRNA in the development of cancers remains relatively unexplored. Here, we discuss the current knowledge of the effects of various chemical carcinogens on miRNA expression.

Cigarette smoke

Lung cancer is one of the most widespread occurring malignancies in the world, and directly attributed to tobacco smoke (World Cancer Report 2014). Tobacco

smoke is one of the most prevalent carcinogens around the world and induces different genetic and epigenetic changes, as well as in miRNA expression (Dhahri et al. 2017). Exposure of rats to tobacco smoke for 4 weeks results in the down-regulation of 126 miRNAs in the lungs, and these miRNAs target critical genes that are involved in cell proliferation, the stress response, apoptosis and angiogenesis (Izzotti et al. 2009). Similarly, Khan et al. (2017) identified 13 miRNAs showed significantly altered expression in cigarette smoke exposure while 25 miRNAs showed significantly altered expression in chewing tobacco exposure in esophageal epithelial cells. Cigarette smoke condensate exposure significantly increased miR-31 expression in normal respiratory epithelia, that mediates Wnt antagonist repression, such as Dickkopf-related protein 1 (DKK1) and Secreted frizzled-related protein 1 (SFRP1), resulting in tumorigenicity of lung cancer cells (Xi et al. 2010). The activation of miR-31 was found promoted mammary stem cell expansion and breast tumorigenesis by suppressing Wnt signaling antagonists (Lv et al. 2017). Additionally, H358-smoke cells chronically exposed to cigarette smoke condensate resulted in miR-146a-5p, miR-141-3p, miR-429, miR-200c-3p up-regulation and miR-148a-3p, miR146b-5p down-regulation. The dysregulated miRNA targets various proteins, such as sorbitol dehydrogenase (SORD), intercellular adhesion molecule 1 (ICAM1), phosphoglycerate kinase 1 (PGK1), whose were identified as a resource to identify potential diagnostic markers and therapeutic targets in non-small cell lung cancer (NSCLC) patients who are smokers (Babu et al. 2018). Nicotine-derived nitrosamine ketone (NNK) is a lung carcinogenic nitrosamine that presents in tobacco smoke. The expression of serum miR-206 and miR-133b was up-regulated in rat of early stage NNK-induced lung carcinogenesis. The over-expression of serum miR-206 and miR-133b could be associated with lung carcinogenesis induced by chemical carcinogen NNK (Wu et al. 2013). Kalscheuer et al. (2008) reported that NNK exposure to Fisher 344 rats decreases the expression of several miRNAs, including miR-34, miR-101, miR-126 and miR-199, in rat lungs and identified the cytochrome P450 family (CYP2A3) as a potential target of miR-126 suggests a mechanism by which NNK exerts and augments its genotoxic potentials in the lung. MiR-34 was recently found to be a direct target of the Bcl-2 (Ji et al. 2008). It is reported that miR-101 reduced cell proliferation and invasion and enhanced apoptosis in endometrial cancer via regulating PI3K/Akt/mTOR (Zhang et al. 2017a, b). The regulation of ITGA3 by the anti-tumor miR-199 family inhibits cancer cell migration and invasion in head and neck cancer (Koshizuka et al. 2017a). N-Nitrosodiethylamine (DEN) is a possible human carcinogen. Hsu et al. (2013) found that the function of miR-122 is down-regulated in DEN-induced cystogenesis. Further this study revealed the protective role of miR-122 by targeting Axl, a receptor tyrosine kinase promotes oncogenesis by facilitating proliferation, migration, invasion, and angiogenesis and inhibiting apoptosis. In addition, Rao et al. (2017) found miR-122 could inhibit proliferation and invasion in gastric cancer by targeting CREB1.

Air pollution

Recently, the World Health Organization has classified air pollution as a prime cause of cancer worldwide (Vijayan et al. 2015). Duan et al. (2017) identified the altered miRNA expression patterns in zebrafish (Danio rerio) model, and Jardim et al. (2009) evaluated the effect of particulate matter on miRNA levels in primary human bronchial epithelial cells. This study showed that the increased levels of miR-494, miR-513a and miR-923 play a crucial role in silencing tumor suppressor genes response to diesel exhaust particles. The putative target mRNAs of miR-494 directly targeted cyclin-dependent kinase 6 (CDK6), and the miR-494/CDK6 axis has a significant tumor-suppressive effect on osteosarcoma (Yuan et al. 2017a, b). MiR-513a regulates apoptosis caused by flammatory cytokine interferon-γ (Gong et al. 2009). Numerous epidemiological studies have associated exposure to traffic-related air pollution (TRAP) with increased risk of lung and breast cancer. The plasma level of miR-145-5p and miR-193b-3p was decreased in TRAP exposed participants. MiR-145-5p has been identified to inhibit the proliferation of non-small cell lung cancer cells by targeting the oncogene c-Myc (Krauskopf et al. 2018). Exposure to anthropogenic volatile organic compounds, including benzene, toluene, xylene and formaldehyde, also alters miRNA expression in mouse lung, such as the up-regulation of miR-125a and miR-466 and the down-regulation of miR-125b (Wang et al. 2014). It is reported that miR-125a suppressed laryngeal squamous cell carcinoma

progression by targeting hexokinase 2, and miR-466 inhibited tumor growth and bone metastasis in prostate cancer by direct regulation of osteogenic transcription factor RUNX2 (Colden et al. 2017; Sun et al. 2017a, b). For miR-125b, regulating MALAT1 expression via Notch1 signaling pathway to regulate cell growth, thus participating in the occurrence and progression of multiple myeloma (Gao et al. 2017). Formaldehyde was defined as a human carcinogen and was found to be possibly associated with nasopharyngeal cancer and leukemia (Lee et al. 2017). Rager et al. (2011) demonstrated that gaseous formaldehyde exposure of human lung epithelial cells in vitro leading miR-10b, miR-33, miR-181a and miR-330 down-regulated. MiR-10b inhibited proliferation, migration and invasion in cervical cancer cells via direct targeting of insulin-like growth factor-1 receptor (Hou et al. 2017). MiR-33a may promote tumor development in human glioma by regulating the expression of its target gene, SIRT6 (Chang et al. 2017). MiR-181a promotes epithelial to mesenchymal transition of prostate cancer cells by targeting TGIF2 (Zhiping et al. 2017). MiR-330 inhibited cell proliferation and enhanced chemosensitivity to 5-fluorouracil in colorectal cancer by directly targeting thymidylate synthase (Xu et al. 2017a, b).

Organic pollutants

Polychlorinated biphenyls (PCBs) are well-known environmental pollutants. The toxicity of PCBs is largely based on compounds within this group that share a structural similarity and a toxic mode of action with dioxin. Elyakim et al. (2010) have found that miR-191 was up-regulated by dioxin in HepG2 cells. Inhibition of miR-191 decreased cell proliferation and induced apoptosis in vitro and significantly reduced tumor masses in an orthotropic xenograft mouse model of hepatocellular carcinoma. TCDD (Dioxin) belongs to a group of halogenated aromatic hydrocarbons and is well known for its carcinogenic properties (Sun et al. 2017a, b; Singh et al. 2012). Polychlorinated dibenzo-p-dioxin is a critical pollutant and carcinogen (Murata and Kang 2018). Elyakim et al. (2010) reported that the expression of miR-191 was increased by dioxin in hepatocellular carcinoma of mice, further suggesting that dioxin plays a significant pathological role via a miRNA-dependent mechanism.

Polycyclic aromatic hydrocarbons (PAHs) are considered to be potential human carcinogens (Li et al. 2017a, b, c, d). Benzo(a)pyrene (BaP) induces the up-regulation of miR-17-5p, miR-20a, miR-22, miR-92, miR-106a, miR-320, miR-494 and miR-638 in neoplastic transformation of human bronchial epithelial cells (Shen et al. 2009). Additionally, Jiang et al. (2011) reported over-expression of miR-106a in the malignant transformation of human bronchial epithelium cells after treatment with BaP. The author used the miR-106a mimic to up-regulate miR-106a activity in malignantly transformed cell-induced cell proliferation, and miR-106a was targeting the tumor suppressor RB1 by bioinformatic analysis. Moreover, the over-expression of miR-638 was examined in peripheral lymphocytes from PAH-exposed workers, that aggravated cell DNA damage induced by BaP, which might induce carcinogenesis by targeting breast cancer 1 (Li et al. 2012a). MiR-22 suppresses tumorigenesis and improves radiosensitivity of breast cancer cells by targeting SIRT1 (Zhang et al. 2017a, b), similarly, Zou et al. found miR-22 inhibits cell growth and metastasis in breast cancer via targeting of SIRT1. With exposure to BaP, the elevated level of miR-34c was consistent with phosphorylated p53. Over-expression of miR-34c resulted in inhibition of the BaP-induced G1-to-S transition and diminished up-regulation of cyclin D, and the up-regulated miR-34c orsilenced cylin D prevented BaP-induced malignant transformation (Han et al. 2014). The aromatic amine 2-AAF, aliver carcinogen, which would inactivate the p53 gene during hepatocarcinogenesis is associated with the anti-apoptotic growth-related genes and pro-apoptotic genes (Pogribny et al. 2009). The expression of miR-18, miR-21, miR-182 and the miR-200 family was up-regulated by the long-term administration of 2-AAF.

Bisphenol A (BPA) is a typical endocrine disruptor and caused the genotoxic damage in the liver and breast (Murata and Kang 2018). It was reported that BPA exposure induces alterations in miRNA levels (Chou et al. 2017). Avissar-Whiting et al. (2010) demonstrated over-expression of miR-146a in a BPA-treated placental cell line and showed that over-expression of miR-146a is associated with suppression of cell proliferation. Expression of miR-134 was down-regulated in mouse embryonic stem cells after treatment with BPA, resulting in increased expression of Oct4, Sox2 and Nanog, which play key roles in

maintaining cells in a pluripotent (Chen et al. 2013). Nonylphenol, a major component of the discharge of effluent from sewage, is a carcinogenic compound classified as an endocrine disrupter. Choi et al. (2011) reported that mouse TM4 Sertoli cells showed significant alterations in 186 miRNAs after treatment with nonylphenol. Studies also showed that exposure to asbestos caused respiratory-tract cancer, and mesothelioma of the lung cancer. The expression of let-7c, miR-16, miR-195, miR-200b, miR-200c, miR-205 and miR-589 was altered in breast cancer MCF-7 and hepatoma HepG2 cell lines, which are treated with nonylphenol (Paul et al., 2009). Perfluorooctanoic acid (PFOA) is a carcinogen and a synthetic perfluorinated carboxylic acid and fluorosurfactant (Wang et al. 2012). MiR-26b and miR-199a-3p were elevated in serum exposure to PFOA. MiR-26b inhibited esophageal squamous cancer cell proliferation through suppression of c-MYC pathway, and miR-199a-3p inhibited cell proliferation and induced apoptosis by targeting YAP1, suppressing Jagged1-Notch signaling in human hepatocellular carcinoma (Li et al. 2017a, b, c, d; Ren et al. 2016). In addition, miR-26b suppressed autophagy in breast cancer cells by targeting DRAM1 mRNA (Meng et al. 2018). Studies have shown that di(2-ethylhexyl) phthalate (DEHP) could disrupt ovarian function, mice were administered DEHP revealed a significantly increased expression of ovarian miRNAs (let-7b, miR-17-5p miR-181a and miR-151), which inhibit follicular granulosa cell proliferation, seggested that long-term and high-dose DEHP exposure may be associated with ovarian cancer (Liu et al. 2018). 7,12-dimethylbenz(a)anthrance (DMBA) is a well-known carcinogen. Recently, one study found that treatment of human hepatocellular carcinoma cells (HepG2) with benzo[a]anthracene and benzo[k]fluoranthene up-regulated miR-181 family members, which plays a critical role in PAH-induced hepatocarcinogenesis by targeting expression of MKP-5, leading p38-mediate MAPK activation (Song et al. 2013). Moreover, the expression of miR-21 and miR-155 was significantly elevated in the lungs and kidneys after DMBA treatment for 6 h (Juhasz et al. 2013). MiR-155 mediated ATO resistance by up-regulating the Nrf2 signaling pathway and suppressing apoptosis in lung cancer cells (Gu et al. 2017).

Metals

Metals, a major category of distributed pollutants, are associated with many health problems including cancer (Zeng et al. 2018). Different studies have demonstrated the relationship between altered miRNA expression and metals exposure such as As, Cd, aluminum (Al) and chromium (Cr) (Choi et al. 2018; Dioni et al. 2017; Xu et al. 2015). Although As is not acting a strong genotoxic carcinogen, it is also well known that As exposure is associated with different cancers including skin, lung, bladder and liver cancers (Saint-Jacques et al. 2014; Sturchio et al. 2014). Recent studies show that arsenic exposure associated with the alteration of histone deacetylase and DNA methyltransferase activity, and epigenetic patterns of gene regulation in cancers (Bjørklund et al. 2017). Along with these studies have demonstrated that arsenite-transformed human bronchial epithelial cells release exosomes containing miR-21, which was associated with malignant transformation (Xu et al. 2015). Ling et al. (2012) found that arsenite treatment of human embryo lung fibroblast cells increased the formation of reactive oxygen species (ROS), which triggered the extracellular signal regulated kinase (ERK)-nuclear factor-kB (NF-κB) pathway activation, resulting in NF-κB directly binds to the miR-21 promoter region and increased miR-21 expression (Priyanka et al. 2017). The authors further found another target of miR-21 was Spry, which negatively regulates the Ras/MEK/ERK pathway, was decreased in arsenite-treated cells (Humphries et al. 2016). Selcuklu et al. (2009) reported miR-21 over-expression in almost all human cancers, including lung carcinogenesis, and up-regulation of miR-21 may contribute to the carcinogenic process by activating the EMT (epithelial–mesenchymal transition) program and targeting the p53 signaling pathway. Moreover, arsenic exposure down-regulated miR-31 and the release of this inhibition caused over-expression of special AT-rich sequence-binding protein 2 (SATB2) (Chen et al. 2018). SATB2 is a prominent transcription factor and implicated in human lung cancer. The over-expression of SATB2 induces malignant transformation of human bronchial epithelial cells indicating the importance of the expression of miR-31 in preventing carcinogenesis by suppressing SATB2. Herbert et al. (2014) found arsenic altered epigenetic regulation of SIRT1 expression via structural reorganisation of

chromatin at the miR-34a gene promoter in the initial 24 h of arsenic exposure, and over time, through shifting in miR-34a and SIRT1 gene methylation. MiR-1228, miR-1254 and miR-645 were differentially expressed after 3- and 7-week chronic low arsenite exposure in human keratinocytes. MiR-1228 was reported to be induced in breast cancer regulated the levels of mRNA and protein of SCAI, miR-1254 was reported to be induced in non-small cell lung cancer, and miR-645 was found to promote cell invasion and metastasis (Al-Eryani et al. 2018).

Beezhold et al. (2011) demonstrated that As^{3+} is capable of inducing miR-190 expression in HBE cells, elevated miR-190 down-regulated the translation of the PH domain leucine-rich repeat protein phosphatase (PHLPP), which enhanced the activation of Akt signaling pathway through miR-190 interacted with the 3′-UTR of the PHLPP mRNA. In human keratinocytes (HaCaT cells), exposed to a low dose of sodium arsenite (1.0 μM) for 15 weeks, leading increases in interleukin-6 (IL-6) and miR-21 levels and activation of activators of transcription 3 ($STAT_3$), which induced the epithelial-mesenchymal transition neoplastic properties, and migratory capacity of arsenite-transformed (human keratinocytes) HaCaT cells (Markou et al. 2016). Cao et al. (2011) also demonstrated that numerous miRNAs are up-regulated or down-regulated in human T24 bladder carcinoma cells exposed to As trioxide. The results of this study also showed As-induced alterations in miRNA expression were reversible when the source of exposure was removed.

Different studies have identified inhaled Cr associated with lung cancer (Choi et al. 2018). Expression of miR-143 was altered in Cr-induced malignant transformation and tumor angiogenesis (He et al. 2013). In another study, it was found that the expression of let-7 was down-regulated in HepG2 hepatocellular carcinoma cells following Cd exposure (Fabbri et al. 2012). The let-7 miRNA family has been proposed to function in tumor suppression because reduced expression of let-7 family members is common in non-small cell lung cancer (Yin et al. 2017). The expression of miR-449-a was reported influenced by Cd and it interacts with proto-oncogene Bcl-2 and inhibits tumor formation (Hu et al. 2014; Weng et al. 2014). However, the molecular mechanism behind the cancer-inducing properties of these metals has not been elucidated clearly.

Other chemical carcinogens

Aflatoxin-B1 (AFB1) was highly toxic and mutagenic. It was reported that AFB1 could induce the high rate of hepatocellular carcinoma. Down-regulation of Drosha, DGCR8 and Dicer 1 indicated the impairment of miRNA biogenesis in response to AFB1 (Zhu et al. 2015). The authors demonstrated AFB1 might down-regulate Wnt/β-catenin signaling pathway in HepG2 cells by up-regulating miR-34a, which may involve in the mechanism of liver tumorigenesis. MiR-34a functions as a tumor suppressor by directly targeting oncogenic phospholipase C elipson 1 (PLCE1) in Kazakh esophageal squamous cell carcinoma (Cui et al. 2017a, b). Hexahydor-1,3,5-trinitro-1,3,5-triazine (RDX) is a synthetic chemical compound widely used in the military and mining industries. RDX has been classified as a class C potential human carcinogen (Zhang and Pan 2009). RDX exposure induced significant changes in miRNA expression profiles, including significant up-regulation of oncogenic miRNAs and a significant down-regulation of tumor-suppressing miRNAs, which included let-7, miR-17-92, miR-10b, miR-15, miR-16, miR-26, and miR-181. Microarray analysis of miRNA expression in propiconazole-treated mice found altered expression of 19 miRNAs in propiconazole-treated rats (Ross et al. 2010). In addition, myclobutanil and tridadimefon fungicides also altered the expression of miRNAs in the HepG2 human hepatocellular carcinoma cell line (An et al. 2013). Drinking water chlorination has also been associated with serious adverse health effects, such as bladder cancer (Nieuwenhuijsen et al. 2009). Chlorine in combination with organic matter yields so-called disinfection by-products (DBPs), the impact of DBP exposure on bladder and colon cancer risk is highly relevant. Interestingly, a short period of swimming in a chlorinated pool can produce changes in miRNA expression. Concordant microRNA/mRNA expressions were identified in association with DBP exposure for hsa-mir-22-3p and hsa-miR-146a-5p and their target RCOR1 and TLR4, both related to colon cancer in association with DBP exposure (Espín-Pérez et al. 2018).

Asbestos is a group of natural crystalline silicates that have been classified by the International Agency for Research on Cancer (IARC) as “carcinogenic to humans” (IARC 2012). Over-expression of miR-205 was detected in the normal samples from asbestos-

exposed patients with squamous cell carcinoma compared with those from nonexposed patients (Nymark et al. 2011). The over-expression of miR-205 correlated with the down-regulation of the target gene DOK4, which was found to be abnormal expression in non-small cell lung cancer and may be involved in cellular growth, signaling, and survival by activating the MAP kinase pathway (Gray et al. 2008). Santarelli et al. (2011) investigated alterations in the expression of miRNA in malignant pleural mesothelioma patients and found that most of the tested miRNAs were down-regulated in cancer patients, and further suggested that the expression levels of miR-126 in serum can serve as a biomarker for identifying developing malignant pleural mesothelioma. Moreover, dysregulated expression of the miR-137 and its target YBX1 contribute to the invasive characteristics of malignant pleural mesothelioma (Johnson et al. 2018). Plasmatic extracellular vesicles miR-30e-3p and miR-103a-3p may help to discriminate between malignant pleural mesothelioma patients and subjects with past asbestos exposure (Tommaso et al. 2017). Weber et al. (2012) identified that miR-103 was characterized by a promising sensitivity and specificity and might be a potential minimally invasive biomarker for the diagnosis of mesothelioma based on the analysis of the blood of mesothelioma patients and asbestos-exposed controls. Vinyl carbamate (urethane) is found in alcoholic beverages and different food products. It is reported that mice treated with urethane miR-21, miR-31, miR-130a, miR-146b and miR-377 were consistently up-regulated, whereas miR-1 and miR-143 were down-regulated in lung tumors relative to normal lungs (Melkamu et al. 2010). Up-regulation of miR-21 caused increased cell proliferation, reduced apoptosis and enhanced tumor growth and invasion by down-regulating the expression of tumor suppressor genes such as PTEN (Meng et al. 2007). MiR-377 was down-regulated in gastric cancer and suppressed cell proliferation, migration and invasion partly via repressing the VEGFA expression, which could provide a potential target for GC diagnosis and therapy (Wang et al. 2017a, b). MiR-130a was down-regulated by curcumin treatment, also inhibited colon cancer by suppressing the Wnt/β-catenin pathways (Dou et al. 2017). MiR-1 can target CCND2 and CXCR4 and is involved in cell proliferation and migration, and modulated multiple cancer processes by influencing oncogenic TAGLN2 in renal cell carcinoma (Kawakami et al. 2012; Leone et al. 2011). However, the plausible mechanisms by which these environmental chemicals alter miRNA expression in different cancers are not fully understood. Details of these findings and altered miRNAs are presented in Table 1.

Mechanisms of chemical carcinogen-induced alterations in microRNA

In this review, we provide evidence that clearly indicates that deregulation of miRNA expression in response to carcinogenic pollutants may be a key event in tumorigenesis. The underlying mechanisms of these carcinogen-induced aberrations plausibly involve different direct and indirect pathways of miRNA biogenesis. Further, these studies demonstrate that exposure to carcinogens can alter both gene expression and epigenetic mechanisms, such as altered cytosine DNA methylation and histone modifications. Recently, Izzotti and Pulliero (2014) reported that exposure to tobacco smoke increased formation of miRNA adducts, compared to DNA adducts, in mice. DNA damage may be the initial reason upon acute or chronic exposure to chemical carcinogens (Xu et al. 2017b). If mutations occurred in oncogenes or tumor suppressor genes, the deregulation of growth and cell function would contribute to carcinogenesis via miRNA function as oncogenes or tumor suppressor genes, particularly in chemical carcinogenesis. MiR-487b is a tumor suppressor miRNA that was down-regulated by cigarette smoke condensate and restrained by epigenetic mechanisms during tobacco-induced pulmonary carcinogenesis (Xi et al. 2013). Interestingly, oncoprotective miRNAs play a crucial role in the initial chemical carcinogenesis. For instance, let-7a represses the expression of the mutated oncogenic KRAS gene (He et al. 2010). In cigarette smoke-exposed mice, in which early over-expression of mutated KRAS occurs, cancer does not occur until let-7a expression is irreversibly down-regulated by long-term exposure to cigarette smoke (Izzotti et al. 2011). Accordingly, the initiation and progression of tumors involve multiple events. As mentioned, miRNA expression is altered by various environmental factors, including air pollution, cigarette smoke, organic pollutants and metals. The putative targets of the altered miRNAs are associated with oxidative stress, xenobiotic metabolism, inflammation,

Table 1 Environmental chemical carcinogens and miRNAs

Chemical carcinogens	Species	MicroRNAs		miRNA function	Diseases and Cancer	References
		Up-regulated (↑)	Down-regulated (↓)			
Cigarette smoke						
	Rat	miR-294	miR-30,let-7,miR-10,miR-26,miR-34,miR-223,miR-122,miR-123,miR-124,miR-99,miR-125,miR-140,miR-145,miR-146,miR-191,miR-192,miR-219, miR-222,	Targets p53, Oncogene, STAT3, Apoptosis	Lung cancer, non-small cell lung cancer	Izzotti et al. (2009) and Wang et al. (2017a, b)
	Mice	Let-7e,miR-19a,miR-191,miR-142,miR-350	miR-92b,miR-668,miR-700	Tumor suppressor, apoptosis	Lung cancer	Yuchuan et al. (2014)
	Mice		let-7f		Vasculardisease	Dhahri et al. (2017)
	Mice	miR-146a-5p,miR-141-3p,miR-429,miR-200c-3p	miR-148a-3p,miR-146b-5p	Targets Src-FAK pathway, kruppellike factor-9, PGK1, ICAM1, SORD	Non-small cell lung cancer	Babu et al. (2018)
	Human	miR-31		Targets Wnt, DKK1, SFRP	Breast cancer, lung cancer	Lv et al. (2017) and Xi et al. (2010)
	Human		let-7i-3p,miR-154-5p	Targets NF-κB, HIF-1, MAPK, Notch	Lung cancer	Huang et al. (2014)
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone						
	Rat	miR-206,miR-133b		Tumor suppressor	Lung cancer	Wu et al. (2013)
	Human		miR-487b	Targets SUZ12, BMI1, WNT5A, MYC, and KRAS	Lung cancers	Xi et al. (2013)
	Human		miR-199,miR-101,miR-126, miR-34,	Targets Bcl-2, YES1	Gastric cancer, prostate cancer	Chen et al. (2017), Ji et al. (2008) and Kalscheuer et al. (2008)

Table 1 continued

Chemical carcinogens	Species	MicroRNAs		miRNA function	Diseases and Cancer	References
		Up-regulated (↑)	Down-regulated (↓)			
N-Nitrosodiethylamine						
	Mice		miR-122	Targets Axl, CREB1	Hepatocellular carcinoma, gastric cancer	Hsu et al. (2013) and Rao et al. (2017)
Air pollution						
Diesel exhaust particles						
	Human	miR-494,miR-513a,miR-923,miR-513a-5p	miR-31,miR-26b,miR-27a,miR-374a	Targets Wnt, p53, TGF-β, DICER, ATM, PTEN, Apoptosis, Tumor suppressor	Lung cancer,	Jardim et al. (2009) and Ris (2007)
Volatile organic compounds						
	Mice	miR-125a,miR-466	miR-125b	Targets RUNX2, Cell proliferation, Apoptosis	LSCC, prostate cancer, lung adenocarcinomas	Gao et al. (2017), Colden et al. (2017), Wang et al. (2014) and Sun et al. (2017a, b)
Benzene-pyridine						
	Human	miR-205		Targets E2F1,ZEB2,ERBB3, anti-tumor	Melanoma	Noguchi et al. (2013)
Traffic-related air pollution						
	Human		miR-145-5p,miR-193b-3p	c-Myc	Lung, breast cancer	Krauskopf et al. (2018).
Formaldehyde						
	Human		miR-10b,miR-33, miR-181a,miR-330	Targets NF-κB, IL-8, IGF-1R, Tumor invasion and metastasis	Nasopharyngeal cancer, Cervical cancer	Hou et al. (2017 and Rager et al. (2011)
	Human		miR-338-5p	Targets BRAF, NRAS, Oncogenic	Melanoma	Caramuta et al. (2010)
	Monkey	miR-152,miR-125b	miR-145,miR-22, miR-26b,	Targets Wnt, p53, Tumor suppressor, Methylation, Apoptosis	Nasal squamous cell carcinomas, Leukemia	Rager et al. (2013)

Table 1 continued

Chemical carcinogens	Species	MicroRNAs		miRNA function	Diseases and Cancer	References
		Up-regulated (↑)	Down-regulated (↓)			
Organic pollutants						
Polychlorinated biphenyls						
	Human	miR-191		OncomiR	Hepatocellular carcinoma	Elyakim et al. (2010 and Guida et al. (2013)
Benzo(a)pyrene						
	Human	miR-638		Targets breast cancer 1, DNA repair	Breast cancer	Li et al. (2012a)
	Mice	miR-34c,miR-34b-5p,miR-29b	miR-150,miR-142-5p,miR-122	Targets MCL-1, Cdkn1a, Oncogene, SPOCK1	Lung tumor, squamous cell carcinoma.	Halappanavar et al. (2011) and Koshizuka et al. (2017b)
	Human		miR-22	Targets SIRT1	Breast cancer	Zou et al. (2017), Zhang et al. (2017a, b)
7,12-dimethylbenz (a)anthrance						
	Hamster	miR-21,miR-200b, miR-221,miR-338, miR-762	miR-26a,miR-124a,miR-125b,miR-126-5p,miR-143,miR-145,miR-148b,miR-29a,miR-155,miR-199a, miR-203, miR-16	Oncogenes	Oral cancer	Yu et al. (2009)
	Mice	miR-21,miR-146a,let-7a		Targetsp53, NF-κB, Ras, c-myc, CCR7/ MAPK	Leukemia, lymphoma, skin and breast cancer, lung cancer, prostate cancer	Guanlin et al. (2017) and Juhasz et al. (2012)
Benzo[a]anthracene,benzo[k]fluoranthene						
	Human	miR-181a,miR-181b, miR-181d		Targets MKP-5, p38 MAPK	Hepatocellular carcinoma	Song et al. (2013)
Polycyclic aromatic hydrocarbon						
	Human		miR-24,miR-27a,miR-28	OncomiR, Apoptosis	Hepatocarcinoma, pancreatic cancer	Cui et al. (2017a, b) and Deng et al. (2014)
	Human	miR-181a/b/c		Targets TGIF2, Apoptosis, oncomiR,	Hepatocarcinoma, prostate cancer	Song et al. (2013) and Zhiping et al. (2017)

Table 1 continued

Chemical carcinogens	Species	MicroRNAs		miRNA function	Diseases and Cancer	References
		Up-regulated (↑)	Down-regulated (↓)			
Perfluorooctanoic acid						
	Human	miR-26b,miR-199a-3p		Oncogene activation	Hepatocellular carcinoma	Wang et al. (2012)
Perfluorooctanesulfonate						
	Rat	miR-23a,miR-25,miR-125a,miR-133b,miR-206,miR-494	miR-451	TargetsLAG1, PTBP2, SERP1, BDNF, FOXP1, PTEN, PI3K/AKT, Oncogene activation, ROS, Apoptosis	Osteosarcoma	Wang et al. (2015) and Yuan et al. (2017a, b)
Tetrachlorodibenzo-p-dioxin						
	Mice	miR-486,miR-122,miR-181a	miR-31,miR-181c,miR-671,miR-466c,miR-134a	Apoptosis, Tumor suppressor	Lung cancer, gastric cancer, breast cancer, ovarian cancer	Liu et al. (2010), Singh et al. (2012) and Yoshioka et al. (2011)
Dioxin						
	Human	miR-191		Targets TGF-β and MAPK pathways	Hepatocellular carcinoma	Elyakim et al. (2010)
BisphenolA						
	Human	miR-222,	let-7 g,let-7f,miR-21,miR-26b, miR-342-3p	Targets Wnt, p53, TGF-β, Tumor suppressor	Breast carcinoma	Tilghman et al. 2012)
BisphenolA and Dichlorodiphenyltrichloroethane						
	Human	miR-638	miR-15b	Targeting Bcl-2, Tumor suppressor	Breast carcinoma	Tilghman et al. (2012)
Metals						
Arsenic						
	Human	miR-21		Targets $STAT_3$	Lung cancer	Markou et al. (2016 and Xu et al. (2015)
	Human	miR-21		Targets Ras/MEK/ERK, ROS	Lung cancer	Humphries et al. (2016) and Ling et al. (2012)
	Human		miR-134,miR-373,miR-155,miR-138,miR-205,miR-181d, miR-181c, let-7	Targets Ras, Oncogenes	Prostate cancer	Ngalame et al. (2014)

Table 1 continued

Chemical carcinogens	Species	MicroRNAs		miRNA function	Diseases and Cancer	References
		Up-regulated (↑)	Down-regulated (↓)			
	Human	miR-21		Targets EMT and p53	Lung cancer	Selcuklu et al. (2009)
	Human		miR-31	Targets SATB2	Lung cancer	Chen et al. (2018)
	Human	miR-190		Targets PHLPP and Akt, OncomiR		Beezhold et al. (2011 and Herbert et al. (2014)
	Human	miR-19b,miR-24,miR-29b		OncomiR, Apoptosis, LASP1	Vascular injury, gastric cancer	Li et al. (2012b, 2017a, b, c, d)
	Human	miR-222	miR-19a	Targets PTEN, Apoptosis	Bladder cancer	Cao et al. 20172011)
Aluminum						
	Human	miR-9		Targets Dicer1, HuR, and CDH1	Hodgkin lymphoma, Breast cancer	Leucci et al. (2012) and Ma et al. (2010)
Cadmium						
	Rat	miR-193,miR-221, miR-222		Targets c-kit, Bcl-2, Oncogene, Apoptosis	Ovarian cancer, Prostate cancer	Weng et al. (2014)
Chromium						
	Human		miR-3940-5p	Targets p53, XRCC2, Tumor suppressor	Non-small cell lung carcinoma	Li et al. (2014)
Other Carcinogens						
Aflatoxin-B1						
		miR-34a		Targets SERP1, PLCE1, BDNF, FOXP1, TNKS-2, Bcl-2, Wnt/β-catenin	Hepatocarcinoma	Cui et al. (2017a, b) and Zhu et al. (2015)
Hexahydro-1,3,5-trinitro-1,3,5-triazine						
	Mice	miR-206,let-7e,miR-15, miR-16	miR-200c,miR-27a	Apoptosis	Lung cancer cell	Takamizawa et al. (2004) and Zhang and Pan (2009)
Propiconazole						
	Mice	miR-135b	miR-466b-5P		Hepatocellular carcinoma	Ross et al. (2010)
Disinfection by-products						
	Human		mir-22-3p,miR-146a-5p	Targets RCOR1 and TLR4	Colon and bladder cancer	Espín-Pérez et al. (2018)

Table 1 continued

Chemical carcinogens	Species	MicroRNAs		miRNA function	Diseases and Cancer	References
		Up-regulated (↑)	Down-regulated (↓)			
Nonylphenol						
	Mice	miR-125a-3p,miR-297c,miR-421,miR-452,miR-483,miR-574-3p,miR-574-5p,miR-669a, miR-720	let-7 g,miR-107,miR-10a,miR-15a,miR-15b,miR-199b,miR-324-5p,miR-331-3p,miR-342-3p, miR-29c, miR-26a	TargetsWnt/β-catenin signaling (Wnt1), ERK/MAP kinase, Apoptosis	Breast cancer	Choi et al. (2011)
Asbestos						
	Human	miR-205		Targets DOK4, MAP kinase	Lung Cancer	Gray et al. (2008) and Nymark et al. (2011)
	Human	miR-30e-3p, miR-103a-3p		Targets Ubc9	Malignant mesothelioma	Tommaso et al. (2017)
	Human	miR-130		PTEN	Malignant mesothelioma	Weber et al. (2012)
	Human	miR-137		YBX1	Malignant pleural mesothelioma	Johnson et al. (2018)
Urethane						
	Mice	miR-21,miR-31,miR-130a,miR-146b,miR-377	miR-1,miR-143	Targets PTEN, tropomyosin 1, p53, PDCD4, RECK, Apoptosis, VEGFA	Lung tumor, Gastric cancer	Melkamu et al. (2010) and Wang et al. (2017a, b)

oncogenesis, and tumor suppression, as shown by a recent demonstration that exposure to ambient particular-matter 2.5 and its metal components altered the expression of miRNAs via increasing oxidative stress and triggering inflammatory responses (Schembri et al. 2009). Ling et al. (2012) reported that miR-21 up-regulation mediated the transformation of human embryo lung fibroblast cells induced by chronic arsenite exposure. Intriguingly, miR-21 is mediated by reactive oxygen species activation of the ERK/NF-κB pathway. These studies mainly show that miRNA regulates target mRNAs significantly in tumor initiation and progression. However, the precise function of miRNAs in chemical-induced carcinogenesis still requires exploration. Indeed, evidence accumulated during recent years has established that miRNA dysregulation may be caused by inaccuracy of miRNA biogenesis, genetic mutations, or epigenetic mechanisms (Kavitha et al. 2014). This hypothesis was evidenced by bioinformatics analysis of environmental carcinogenesis which formed miRNA adducts and modified the structure of miRNAs by blocking their access to the catalytic pockets of Dicer and altered the maturation process. According to this study, DNA damage influences miRNA expression via a p53-dependent mechanism. Furthermore, molecular and cellular pathways are also involved in alterations in miRNA expression. All these miRNA expression changes are related to increased cell proliferation and inhibition of apoptosis, and may be the underlying mechanism of imbalance between cell proliferation and apoptosis during tumorigenesis. However, these situations clearly indicate other mechanisms that cause alterations in miRNA expression should be taken into account. The dysregulation of miRNA expression is particularly apparent responses to environment stimuli in tumor, consequently contributing to oncogenesis and cancer progression. In this review, the occurrence of miRNA alterations indicates their significance to cancer development. In addition, the precise mechanisms behind miRNA dysregulation in environmental stimuli might provide new insights for understanding the mechanisms of chemically induced tumorigenesis and the treatment of cancer (Fig. 2).

Conclusion and future directions

The evidence highlighted in this review illustrates the alterations of miRNAs expression in response to environmental chemical carcinogens and their target genes may be a key event in tumorigenesis. Until now, it has been demonstrated that miRNA alterations occur to various chemical exposure, and the specific altered miRNA maybe as biomarker of chemical carcinogens exposure. Further, it is not specific that early miRNA alteration in response to chemical carcinogens for cancer progression. The possible reasons may be simply being one of the transitory non-specific cellular responses to chemical treatment. However, to establish a link between miRNAs and carcinogenesis, an approach should be applied to appraise the role of chemical-induced miRNA alterations and its target genes in the carcinogenic process. There have been very few studies that assemble a detailed catalog of target genes of various miRNA responses to chemical carcinogens exposure. This could be due to the majority of experiments focused on the relationship between environmental chemical exposure and miRNAs expression, rather than the underlying mechanisms. Our review provides a list of altered miRNAs in response to environmental chemical carcinogens, including oncomiRNAs and oncoprotective miRNAs. Typical oncomiRNAs, such as miR-21, miR-33a, miR-155 and miR-181a, which targets have been identified with SIRT6, PTEN, Nrf2 and TGIF2 gene whose suppression involves in cell apoptosis, proliferation, invasion and metastatization. Oncoprotective miRNAs, such as let-7a, miR-22, miR-266, miR-466 and miR-499a, whose main targets have been identified with gene products which related the expression of the mutated oncogenes (Fig. 1). While it is difficult to identify the interaction of miRNA and miRNA targets (oncogene or anti-oncogene) during cancer progression upon carcinogens exposure. The plausible mechanisms by which these environmental chemicals alter the miRNAs expression of different cancers are not fully understood. Emerging evidence suggests that aberrant miRNA expression during carcinogenesis may be associated with epigenetic abnormalities and different molecular pathways. Investigation of DNA methylation patterns, histone modifications, mitochondrial damage, and inflammation, as well as oxidative stress, may be helpful for a better

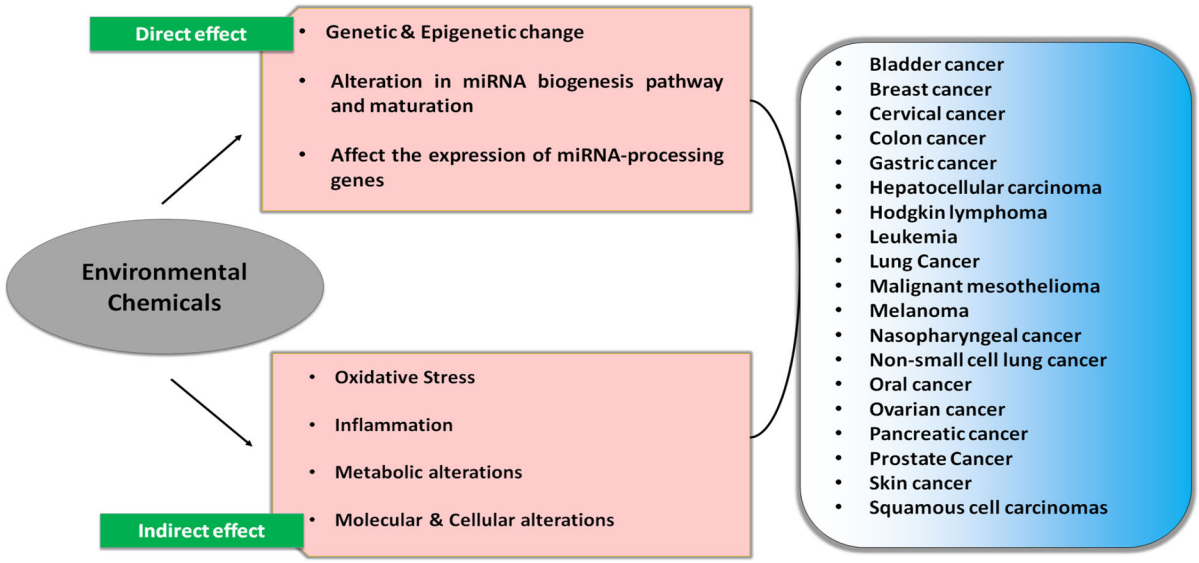

Fig. 2 Direct and indirect pathway mechanisms of environmental chemically induced cancers. The underlying mechanism of carcinogen exposure and cancer is probably due to carcinogens directly affect the genetic and epigenetic change, alteration in miRNA biogenesis pathway and the expression of miRNA-processing genes. Furthermore, the indirect effect of carcinogens on chemicals exposure induces oxidative stress, inflammation, metabolic, molecular and cellular alterations

understanding of mechanisms associated with chemical-induced cancers.

This review clearly indicates the alteration of miRNA expression following exposure to environmental chemical carcinogens is a future direction for early indicators of the carcinogenic process. Since the discovery of circulating miRNAs in body fluids, extracellular miRNAs have potential as noninvasive biomarkers for the prediction and prognosis of cancer and are showing great prospects for the clinical application of circulating miRNAs as predictors for diseases, particularly for cancers. However, the application of miRNA as biomarkers in tumor diagnosis and therapeutic responses to environmental toxicants is still extremely challenging for clinical application. Several major observations should be taken into accounts in further future studies that the effects of age and gender on miRNA profiles in response to chemical carcinogens. Additional studies with well-documented patient samples will be needed to address this question. At present little is known about whether environmental chemicals exposure induces long-term changes in miRNA expression or whether these have a transient character. The changes from reversibility to the irreversibility of miRNA alterations depend on both dose and duration of exposure. Therefore, more longitudinal studies should be conducted to examine the long-term effects of chemical carcinogens on the role of miRNAs in the development and pathogenesis of various cancers. In conclusion, this review will enhance our understanding of the role of miRNA in various cancers induced by environmental chemicals, further suggesting that an investigation of the relationship between miRNA alterations and environmental carcinogens will provide future directions for cancer prevention.

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