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Review

MicroRNAs in inflammation and response to injuries induced by environmental pollution

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ABSTRACT

MicroRNAs (miRNAs) are small noncoding RNAs that regulate basic biological processes by posttranscriptional suppression of their target genes. Altered miRNA expression may lead to widespread gene expression changes and has been implicated in pathophysiological processes such as cancer and inflammation. In this review, we summarize the present knowledge about the role of miRNAs in inflammation and in the response to environmental agents and pollutants, such as cigarette smoke, ethanol, carcinogenic chemicals such as benzo(a)pyrene (BaP) and dioxin, and UV radiation.

Contents

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1. Introduction

MicroRNAs (miRNAs) are small, approximately 19–23 nt long, single-stranded non-coding RNAs that are encoded in the genome and regulate the expression of protein-coding genes [1]. MiRNAs have been implicated in the regulation of a wide variety of biological processes including development, cell differentiation and proliferation, as well as immunity and inflammation [2]. In this review, we will provide an overview of the involvement of miRNAs in inflammation and we will summarize the current knowledge on the association of miRNAs with exposure to environmental pollutants.

The first miRNA, named lin-4, was discovered in *Caenorhabditis elegans* in 1997 [3,4]. This gene regulated developmental transitions [4] and did not code for a protein but a long, non-protein coding transcript, which was processed into small functional RNAs. These small RNA molecules repressed the production of the lin-14 protein at the posttranscriptional level. Although at the time of this discovery, lin-4 was thought to be an exception, a few years later, hundreds of similar small functional RNAs were discovered in every multicellular organism analyzed, including plants, nematodes, arthropods and vertebrates [5]. In 2001, the term "miRNA" together with a systematic nomenclature was officially introduced to designate newly discovered small RNA-coding genes whose function is the regulation of protein-coding genes [5–7]. Today, we understand that miRNAs represent a novel layer in the regulation of the flow of genetic information and cellular functions. Similar to transcription factors, miRNAs are a critical component of the complex system, which defines the rate by which genetic information is expressed.

MiRNAs are encoded in the genomic DNA, and most of them are transcribed by RNA polymerase II. The produced long primary transcript (from few hundred to few thousands bases; *pri-miRNA*) is sequentially processed first in the cell nucleus and then in the cytoplasm to generate the mature, biologically active miRNA [8]. First, an RNase III enzyme, Drosha cleaves the primary transcript in the nucleus and generates an approx. 70 nt long RNA hairpin (*pre-miRNA*), which is then exported into the cytoplasm by Exportin 5. Another RNase III enzyme, Dicer, cleaves the miRNA hairpin into an approximately 22-mer RNA duplex. Most often only one of the two strands becomes the mature miRNA via separating from the other strand and incorporating into the RNA Induced Silencing Complex (RISC). This RNA-protein complex can bind to the 3′ untranslated region (3′UTR) of protein coding mRNAs present in the cytoplasm of the host cell and inhibit protein production via translational suppression, RNA-cleavage, or a combination of these two mechanisms [5,8]. Of note, not all nucleotides of the ~22 nt long miRNA participate in the base-paring, but 6–8 nt of the 5′ end of the miRNA (called the "seed") has a predominant role in defining the interaction, while the remaining nucleotides have complementary roles in this process [9].

A particularly interesting feature of miRNA-mediated gene regulation is that one miRNA can have dozens if not hundreds of functional targets within a cell type [6,7], each carrying the complementary sequences to the miRNA seeds in their 3′UTRs. To further add to the complexity of miRNA-mediated gene regulation, not only can one miRNA regulate hundreds of targets, but also each target can be regulated by multiple miRNAs simultaneously. This is made possible by the fact that mRNAs with long 3′UTRs may contain dozens or more miRNA binding sites [10]. The effect of multiple miRNAs targeting the same mRNA may be additive or synergistic, resulting in a higher degree of inhibition. In some aspects, the action of miRNAs can be compared to the action of transcription factors in terms of pleiotropy, although they act on different levels in the flow of genetic information.

Although bioinformatic predictions suggest that most of the genes are subject to miRNA-mediated regulation, there seem to be exemptions [10]. Genes which need to be transcribed constitutively at a high level, such as house-keeping genes, or antimicrobial peptides necessary in large amounts after induction, tend to have very short 3′UTRs presumably to avoid interference with miRNAs. Interestingly, cells can change the set of 3′UTRs utilized by mRNAs when they undergo activation. A large part of the transcripts in activated T cell switches to alternative set of 3′UTRs, most of which are shorter than the canonical ones, presumably to avoid miRNA-mediated regulation during T cell activation [11]. Recently it has been found that some pseudogenes (i.e. dysfunctional relatives of known genes that have lost their protein-coding ability and are generally thought to have no biological function) are expressed in tumor cells and can regulate the expression of their coding "pair" by luring away miRNAs targeting the corresponding region of the coding mRNA [12].

Since their discovery, miRNAs have been implicated in virtually every biological process investigated. MiRNAs regulate development, organogenesis, basic biochemical processes, signal transduction, cell proliferation, apoptosis and migration/invasion. Shortly after their discovery in human, deregulated miRNA expression was found in disease states such as cancer [13–18], developmental abnormalities [19], muscular [20,21] and cardiovascular disorders [22,23], schizophrenia [24] and in immune-mediated and inflammatory diseases [25–27]. More recently, miRNAs have also been implicated in the cellular response to environmental agents and associated diseases.

Since the 1970s there has been increasing global concern over the public health impacts attributed to environmental pollution. The World Health Organization (WHO) estimates that about a quarter of the diseases facing mankind today occurs due to prolonged exposure to environmental pollution. Several environmental chemicals including benzo(a)pyrene, dioxin, furan and conazoles are known to be carcinogenic, and exposure to ultraviolet (UV) radiation is a major risk for skin cancer. Exposure to airborne particulate matter (for example from diesel exhaust) has been associated with cardiovascular and respiratory diseases [28]. The adverse health effects of cigarette smoke are well-known and include smoking-related malignancies, chronic obstructive lung disease and cardiovascular diseases [29,30]. The mechanism by which these environmental exposures lead to impaired health and diseases is only partially known. While the capability of environmental exposures to produce DNA mutations has been a landmark for risk assessment and prevention, recent evidence suggests that some environmental factors cause epigenetic changes which may increase the risk of disease [31]. Most recently, environmental factors mentioned above have been linked to altered miRNA expression suggesting that miRNAs may be involved in the adverse health effects of these exposures.

2. MiRNAs in inflammation

The involvement of miRNAs in the regulation of immune system development was established already a few years after the discovery of miRNAs [32]. Not only can miRNAs regulate linage commitment during hematopoiesis, but they can also regulate the innate and adaptive immune responses upon encounter with pathogens or antigens, respectively [33–35]. In parallel with the investigation of their roles in the basic immune function, the attention of researchers turned to their potential roles in diseases in which the immune system malfunctions: chronic inflammatory conditions of various organs [2,26,36].

The first studies focused on the identification of deregulated miRNAs in various inflammatory diseases in comparison to

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corresponding healthy organs/tissues. A miRNA expression profiling study revealed deregulated miRNA expression in the skin lesions of patients with psoriasis and atopic dermatitis, two common chronic inflammatory diseases with different immunopathology [25]. This study identified miRNAs with similar regulation in these two diseases, suggesting a general role for these in inflammatory processes, but also disease-specific miRNAs. Further studies identified deregulated miRNAs rheumatoid arthritis, [37], systemic lupus erythematosus [38], multiple sclerosis [39], type I diabetes [40] and ulcerative colitis [41]. In accordance with our view that chronic inflammatory diseases have several shared components in their pathophysiology irrespective of the affected organ, a number of commonly dysregulated miRNA have been identified in many diseases, while other microRNAs are more disease-specific. The role of a few selected miRNAs in inflammation is discussed below.

2.1. MiR-146

MiR-146 was among the first miRNAs to be implicated in the regulation of immune functions [33]. This miRNA is induced by bacterial superantigens and pro-inflammatory cytokines in an NF-κB dependant manner and targets two members of the TLR/IL-1β signal transduction pathway [25,33]. Increased miR-146 expression was found in psoriasis skin lesions [25], in synovial tissue and leukocytes in rheumatoid arthritis patients [37,42,43], and in osteoarthritis [44], in accordance with the fact that the NF-κB pathway is activated in a number of inflammatory disorders. Recent evidence suggests that miR-146 can suppress the production of inflammatory cytokines/chemokines [45] suggesting that it acts as a negative regulator of inflammatory cytokine production. Thus, miR-146 may represent the effector arm of a negative regulatory feedback-loop in inflammation: it is induced by pro-inflammatory cytokines/bacterial products and in turn it suppresses the cytokine response presumably to prevent tissue damage due to excess of inflammation. Interestingly, in systemic lupus erythematosus, miR-146 is down-regulated and correlates with disease severity [46]. The seemingly opposite roles for miR-146 in inflammation indicate the complexity of miRNA functions and the fact that miRNAs may have very different functions depending on cell type and context.

2.2. MiR-21

MiR-21 is an oncogenic miRNA, which is often overexpressed in solid tumors [47]. In T cells, miR-21 is induced upon T cell receptor (TCR) engagement and is supposed to control T cell activation by targeting RASGRP1, a key regulator in TCR signal transduction [2,48]. Moreover, miR-21 is induced by LPS in mouse lung [34] and it has been shown to be induced in several inflammatory diseases including psoriasis, atopic eczema/dermatitis [25], a murine asthma model [49] and ulcerative colitis [50]. Results from the study by Lu et al. identifying miR-21 in an IL-13-induced asthma model suggest a mechanism by which this miRNA may be involved in the regulation of allergic airway inflammation. They identify IL-12p35, a subunit of IL-12, as a target for miR-21. IL-12 is a key cytokine in adaptive immune responses involving Th1 cell polarization. These results imply that miR-21 is involved in inflammation through, at least in part, by modulating cytokine responses and TCR signal transduction. Interestingly, recent evidence suggests that miR-21 may be one of the miRNAs that link inflammation to cancer. Iliopoulos et al. showed that STAT-3 can induce miR-21 that in turn targets PTEN and CYLD tumor suppressors; hence, miR-21 is part of the positive feedback loop that underlies the epigenetic switch initiated that links inflammation to carcinogenesis [51].

2.3. MiR-126

Exposure of sensitized individuals to house dust mite allergen results in airway inflammation and worsens asthmatic condition. In a mouse model of asthma, house dust mite allergens induced the expression of several miRNAs, including miR-21 and miR-126 [52]. Mattes et al. showed that administration of miR-126 inhibitors into asthmatic mice suppressed the asthmatic phenotype, and resulted in diminished Th2 responses, inflammation, airways hyperresponsiveness, eosinophil recruitment, and mucus hypersecretion. These results indicate a functional role for miR-126 in asthma pathogenesis and suggest that interference with miRNA expression may have a therapeutic potential in treating asthma.

2.4. MiR-155

MiR-155 is a multifunctional miRNA that has been implicated in both cancer and inflammation. Similar to miR-21, miR-155 is frequently overexpressed in cancer and functions as an oncogene [53]. In addition, miR-155 is essential for normal immune homeostasis and is involved in the regulation of innate and adaptive immunity [38,54–56]. Along with miR-146, miR-155 is regulated by LPS in an NF-κB dependant manner. Moreover, miR-155 is induced during T cell activation by T cell specific stimulants or superantigens [57].

In line with its high expression in activated T cells, miR-155 has been shown to be up-regulated in several inflammatory diseases, including rheumatoid arthritis [37], ulcerative colitis [50], Helicobacter pylori-induced gastric inflammation [58] and recently in atopic eczema/dermatitis [57].

One of the recently identified targets of miR-155 is cytotoxic T lymphocyte antigene-4 (CTLA-4) a negative regulator of T cell activation, induced by T cell activation signal [57]. Its primary function is to prevent excess of T cell activation and thereby tissue damage and autoimmunity upon physiological T cell activation. Elevated levels of miR-155 in T cells results in suppressed CTLA-4 protein levels and thereby may interfere with a physiological feedback mechanism, which self-limits T cell activation. In accordance, ectopic overexpression of miR-155 in primary human T cells resulted in increased cell proliferation [57].

While miR-155 may contribute to sustained T cell activation, in other cell types it may suppress inflammation. In macrophages and in dendritic cells miR-155 targets several genes in LPS signaling (FADD, IKKε, Rip1 and TAB2) suggesting that miR-155 is involved in negative regulation of the TLR pathway [38,54,59,60]. Recently myeloid differentiation protein 88 (MyD88), an important adapter protein in the TLR/IL-1 pathway was identified as a target of miR-155 [61], supporting a role for miR-155 as a negative regulator of inflammation.

These results suggest that miR-155 up-regulation may have different functional consequences in different tissues/cell types: it seems to enhance the proliferative response in lymphocytes, while it suppresses inflammatory signaling in the myeloid cells. Interestingly, the level and duration of miR-155 expression also has a detrimental role on whether it functions as an oncogene or immunostimulatory molecule. The permanent upregulaton of miR-155 during prolonged inflammation may be a link to cancer [62]. Elucidation of the functional role in miR-155 in inflammatory diseases will require further studies.

The list of miRNAs deregulated in inflammatory diseases is growing every year. Interestingly, some of the de-regulated miRNAs (for example miR146, miR-21, miR-155) seem to be parts of negative feedback mechanisms through the suppression of their target genes. Future investigation will be needed to validate whether they have a causative role in these diseases and whether they can become therapeutic targets.

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Table 1
MicroRNAs regulated by environmental pollutants.

Environmental agent	MicroRNA	Regulation	Cell/tissue type	Species	Reference
Cigarette smoke	let-7c	Down	Lung	Rat	[65,72]
	miR-34c	Down	Lung	Rat	[65]
	miR-222	Down	Lung	Rat	[65]
	let-7f	Down	Lung	Mouse	[71]
	miR-218	Down	Bronchial epithelial cells	Human	[70]
	miR-128b	Down	Bronchial epithelial cells	Human	[70]
	miR181d	Up	Bronchial epithelial cells	Human	[70]
	miR-500	Down	Bronchial epithelial cells	Human	[70]
BaP	miR-494	Up	Bronchial epithelial cells	Mouse	[77]
	miR-320	Up	Bronchial epithelial cells	Mouse	[77]
Anti-BPDE	miR-494	Up	Transformed bronchial epithelial cell line	Human	[75]
	miR-10a	Down	Transformed bronchial epithelial cell line	Human	[74]
	miR-320	Up	Transformed bronchial epithelial cell line	Human	[74]
Diesel exhaust	miR-513	Up	Bronchial epithelial cells	Human	[86]
	miR-923	Up	Bronchial epithelial cells	Human	[86]
	miR-494	Up	Bronchial epithelial cells	Human	[86]
	miR-96	Down	Bronchial epithelial cells	Human	[86]
Participate matter	miR-222	Up	Leukocytes	Human	[88]
	miR-21	Up	Leukocytes	Human	[88]
UV-A	miR-21	Up	Keratinocytes	Human	[96]
	miR-203	Up	Keratinocytes	Human	[96]
	miR-205	Up	Keratinocytes	Human	[96]
UV-B	mir-24	Up	NIH3T3 fibroblast cell line	Mouse	[93]
	miR-21	Up	NIH3T3 fibroblast cell line	Mouse	[93]
	miR-376b	Up	NIH3T3 fibroblast cell line	Mouse	[93]
	let-7a	Up	NIH3T3 fibroblast cell line	Mouse	[93]

3. MiRNA regulation by environmental pollutants and toxins

Environmental toxins and contaminants induce molecular changes, which lead to inflammation and cancer. Since deregulation of miRNAs has been associated with inflammation as well as with cancers in which they regulate tumour growth, survival and metastasis [16,63,64], it is conceivable that miRNAs may be involved in the pathogenic effects of exogenous stimuli. In recent years, the first studies investigating miRNA response to various environmental stimuli appeared; these are reviewed below and the most validated ones are summarized in Table 1.

3.1. MiRNAs associated with toxin exposure in the airways

3.1.1. Cigarette smoke

Cigarette smoke contains >4000 chemical toxins or intoxicants. The most common and well-known tobacco toxins are nicotine, carbon monoxide, formaldehyde, hydrogen cyanide, sulfur dioxide, nitrogen oxide, ammonia, polycyclic aromatic hydrocarbons, and the nitrosamines [30]. The adverse health effects of cigarette smoke are partially due to the direct carcinogenic and oxidative effect of toxins but cigarette smoke has also – less well studied – effects on the immune system.

The first study implicating miRNAs in the effects of cigarette smoke appeared in 2009, when Izzotti et al. showed the deregulation of 126 out of 484 miRNAs in the lung of rats exposed to environmental cigarette smoke [65]. The majority of the altered miRNAs were downregulated, which is consistent with previous findings showing mainly upregulation of mRNA and protein expression in cigarette smoke-exposed lungs (Table 1) [66]. The downregulated miRNAs regulate stress response, apoptosis (e.g. miR-34), proliferation (e.g. let-7 family, miR-125b), inflammation (e.g. miR-30a, miR-146, miR-155), and angiogenesis (e.g. miR-123, miR-222), biological processes that are involved in the pathological effects of cigarette smoke in the lung. Since the suppression of let-7 leads to increased cell proliferation [67], down-regulation of the let-7 miRNAs by cigarette smoke may represent an early step in the development of lung cancer. Indeed, down-regulated let-7 expression is a common finding in solid tumors, including lung cancer [68]. Thus, let-7 may be one of the molecular links connecting cigarette smoke exposure with lung cancer. Strikingly, cigarette smoke dysregulates miRNA expression not only in murine lung but also in the liver [69].

Another recent study investigated the effect of cigarette smoke on miRNA expression in the human lung [70] by comparing miRNA expression in human airway epithelial cells from smokers and never smokers. The study has identified 28 differentially expressed miRNAs, with the majority being downregulated (Table 1)[70]. Of note, the rodent orthologues of several miRNAs downregulated in smokers were found to be downregulated by cigarette smoke in mouse and/or rat lungs (e.g. miR-30, miR-99, miR-125, miR-146, miR-223, miR-218) [65,69,71], indicating the rodent and human lung react in a similar fashion to this exposure.

One of the top downregulated miRNAs was miR-218, which regulated MAFG, a transcription factor whose binding sites were overrepresented among genes regulated in smokers. MiR-218 down-regulation may thus contribute to smoking-dependent changes in the lung.

The role of miRNAs in cigarette smoke-induced inflammation is more controversial: surprisingly, several inflammation-associated miRNAs (e.g. miR-146, miR-155) are downregulated, although cigarette smoke exposure is associated with inflammatory processes in the lung [65].

Interestingly, cigarette-smoke-induced miRNA changes can partially be prevented by a number of chemopreventive agents, suggesting that miRNAs may serve as biomarkers for cancer chemoprevention [72]. However, to date, little is known about how (i.e. induction of changes at the cellular level, or inducing tissue remodelling) cigarette smoke regulates miRNA expression in the lung.

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3.1.2. Benzo(a)pyrene

Benzo(a)pyrene (BaP) is a member of the polycyclic aromatic hydrocarbon (PAH) family, which are environmental contaminants abundantly present in coal tar, cigarette smoke, and even in smoked food. Benzo(a)pyrene is a powerful mutagen and carcinogen, and exposure to BaP is associated with increased risk of lung and cervix cancer [73].

Recent studies have addressed the role of miRNAs in BaP induced carcinogenesis. In a human bronchial epithelial cell line transformed by anti-BPDE, the most important metabolite of BaP, miRNA profiling showed that 45 miRNAs were upregulated and 9 were downregulated [74] (Table 1). Among the downregulated miRNAs was miR-10a, a miRNA previously associated with cancer. One of the upregulated miRNAs was miR-494, also confirmed in a recent study [75] showing that upregulation of miR-494 in the transformed cells leads to the suppression of the tumor suppressor phosphatase and tensin homolog (PTEN). Based on these results, one possible mechanism for BaP-induced carcinogenesis may be upregulation of miR-494, leading to the down-regulation of the tumor suppressor PTEN. Indeed, Moreover, miR-494 is upregulated in small-cell lung cancer [76], and at the same time PTEN is known to be downregulated in lung cancer and correlated with survival.

Although the cells used in this study were malignantly transformed, another study showed that BaP exposure also upregulates miR-494, and another miRNA, miR-320 [77] (Table 1). Up-regulation of miR-494 by BaP may also be protective: its inhibition relieved cells from BaP-induced G1 arrest in bronchial epithelial cells, suggesting that up-regulation of these miRNAs by BaP may contribute to the G1 arrest allowing cells to repair the damaged DNA [77] .

However, miR-320 has not been shown to be differentially expressed in the bronchial epithelium of smokers [70], suggesting that chronic exposure to smoke may have different effects as compared to acute exposure in high concentrations. The effect of chronic smoke exposure on miR-494 is not known and will require further investigation. Moreover, further studies will be needed to clarify the potential role of the miRNAs in the carcinogenic effect of BaP *in vivo*.

3.1.3. Occupational coal dust

Coal workers' pneumoconiosis is a lung disease produced by the inhalation of occupational coal dust. It is characterized by the accumulation of inflammatory cells in the lung, thickening of the alveolar walls and formation of fibrotic nodules. In addition to coal dust exposure, genetic susceptibility is supposed to have a role in the development of the disease, since only part of the exposed individuals is affected [78]. A recent study revealed that a polymorphism (rs2292832) in the pre-miR-149 gene is associated with a significantly increased risk of pneumoconiosis [78]. miR-149 has been proposed to be oncogenic in renal cell carcinoma [79]; however, its role in the lung is as yet unknown and the effect of the identified SNP on miR-149 expression has not been investigated. To clarify whether and how genetic variation in miR-149 contributes to pneumoconiosis further studies will be needed.

3.2. Regulation of miRNAs in the liver by environmental toxins

The liver is a major site for toxicant metabolism, and exposure to various toxins is associated with gene expression changes in the liver. Recent studies have investigated miRNA expression in the liver after exposure to toxins.

3.2.1. Benzo(a)pyrene and dioxin

In contrast to the extensive changes in miRNA expression in bronchial epithelial cells exposed to BaP (see above), miRNA expression remained unchanged in mouse liver after oral exposure to BaP, despite widespread changes in mRNA expression [80]. Lack of change in miRNA expression has been confirmed by two different array platforms as well as qRT-PCR and suggest that miRNA expression the liver is not responsive to BaP *in vivo*. Interestingly, another *in vivo* study showed that miRNA expression in mouse and rat liver was also unresponsive to dioxin (TCDD, 2,3,7,8-tetrachlorodibenzo-7-dioxin) [81]. Of note, TCDD operates via the arylhydorcarbon (AHR) receptor, which is also a receptor for BaP. Hence it is possible that liver miRNAs are not involved in AHR-mediated processes; alternatively that they are in general irresponsive to toxins – despite the fact that the liver is a major site for toxicant metabolism. Future studies including exposure to several different types of toxin will be needed to clarify whether the observed lack of regulation is general or specific to the studied toxins in the concentrations used.

3.2.2. Furan

Furan is an organic compound that is commonly found in foods that undergo heat treatment, including canned and jarred foods, and baby food containing meat. Furan is a potent carcinogen in rodents, although the mechanism of carcinogenicity is not well understood. In a study analyzing mRNA and miRNA changes by PCR array after low dose furan exposure in rats [82], 11 miRNAs were found to be down-regulated (e.g. let-7e, miR-489, miR-296) and 2 miRNAs up-regulated (let-7a, miR-28) in the liver. Changes in miRNA expression were accompanied by expression changes in genes controlling cell cycle and apoptosis. Results of this study suggest that miRNA-mediated regulation may contribute to the carcinogenic effects of furan; however, the potential roles of miRNAs in furan-induced carcinogenesis need to be explored in further studies.

3.2.3. Conazoles

Conazoles are antifungal agents used in agriculture. Some conazoles induce liver tumors in mice, while others are not hepatotumorigenic. A study, aiming to determine the molecular background of conazole tumorigenicity, analyzed miRNA expression by PCR array in mouse liver after oral exposure to tumorigenic (triadimefon and propiconazole) or nontumorigenic (myclobutanil) conazoles for 90 days [83]. Interestingly, the tumorigenic conazoles induced many more changes in miRNA expression (63 and 28 regulated miRNAs, respectively) than the nontumorigenic conazole (1 regulated miRNA). Moreover 19 miRNAs were regulated in the same way by triadimefon and propiconazole, suggesting a role for these miRNAs in the tumorigenic process. Interestingly, these miRNAs are not among those typically identified in liver cancer. Whether the identified changes may be early markers of carcinogenesis will need to be established in future studies.

3.3. MiRNA response to particulate matter exposure

Exposure to particulate matter (PM) in the polluted air has been associated with adverse health outcomes, including cardiovascular and respiratory diseases [84,85]. The largest single source of vehicular-emitted airborne particulate matter is diesel exhaust. Exposure to diesel exhaust particles has been linked to lung cancer and pulmonary inflammation, susceptibility to respiratory infections, exacerbation of asthma and chronic obstructive pulmonary diseases [28]. The molecular mechanisms how diesel exhaust may trigger development of these diseases remains elusive. A recent study showed exposure to diesel exhaust particles had a dramatic effect on miRNA expression in human bronchial epithelial cells: the expression of 197 of 313 detectable miRNAs changed significantly [86]. Thus the extent of changes in miRNA expression is similar to that induced by cigarette smoke [70]. MiR-513,

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miR-494, miR-923 were among the up-regulated miRNAs, while miR-96 decreased (Table 1). The function of the regulated miRNAs in bronchial epithelium is unknown, however based on target prediction and network analysis the authors suggest that the diesel exhaust particle-regulated miRNAs may be involved in the regulation of inflammatory pathways and tumorigenesis. Of note, miR-494 was also found to be up-regulated in bronchial epithelial cells transformed by anti-BPDE [74], suggesting that this miRNA may be involved in the pathogenic effect of several pollutants. Future functional studies will be needed to understand the potential role of miRNAs in adverse health effects of diesel exhaust.

Inhalation of particulate matter causes gene expression changes in peripheral blood of exposed individuals, in particular genes related to inflammatory pathways and oxidative stress have altered expression after particulate matter exposure [87]. To determine whether PM can induce changes in miRNA expression, Bollati et al. analyzed the expression of miR-21, miR-222 and miR-146a in blood leukocytes of foundry workers on the first workday and after 3 days of exposure [88]. Particulate matter exposure induced miR-222 and miR-21 while it had no effect on miR-146a expression (Table 1). MiR-222 and miR-21 have been associated with nitric oxide signaling and response to ROS production, respectively, suggesting that the upregulation of these miRNAs may be due to oxidative stress. Interestingly, miR-222 correlated positively with lead exposure, while there was a negative correlation between miR-146a and exposure to lead and cadmium, indicating a role for metals in inducing molecular changes after PM exposure. Unfortunately, this study measured only the short-term effects of particulate exposure and did not include a control population without any exposure to particulate matter. Using such a control population to compare with exposed individuals would help in defining whether chronic exposure to particulate matter affects miRNA expression and whether altered miRNA expression contributes to the adverse health effects of PM.

A recent *in vivo* study demonstrated that particulate matter exposure affects miRNA expression not only in peripheral blood leukocytes, but also in the myocardium [89]. Exposure to high-concentration metal-rich PM led to a decrease in the expression of 14 out of 113 miRNAs in the myocardium of exposed rats. Interestingly, no miRNAs were upregulated, in keeping with the results of Izzotti et al showing mainly downregulation of miRNAs in the cigarette-smoke exposed lung [65]. The muscle-specific miRNAs miR-1 and miR-133 were identified among the regulated miRNAs both of which have essential roles in heart development and have been associated with heart pathologies [90]. Several inflammation-associated miRNAs were also regulated such as miR-125, miR-146 and miR-150. The precise role of specific miRNAs in PM-mediated cardiac dysfunction remains to be determined.

4. The effect of UV radiation on miRNA expression

UV light is an electromagnetic radiation emitted from the sun (or artificial sources). According to wavelength, UV light can be divided into UV-A (315–380 nm), UV-B (280–315 nm), and UV-C (190–280 nm) [91]. The ozone layer absorbs the most harmful component of UV light, UV-C, and most of UV-B, and it is estimated that 1–10% of UV radiation on the surface of Earth is UV-B and over 90% UV-A [92]. UV radiation causes fundamental cellular and molecular changes, including DNA damage and affects immune functions. In the skin, excess UV irradiation is a major risk factor for skin cancer. In addition, UV light can cause skin inflammation, immunosuppression and promotes ocular diseases. Since miRNAs have been shown to be involved in apoptosis and DNA damage responses as well as immune functions, the question arose whether part of the widespread cellular changes caused by UV radiation may be mediated by miRNAs.

The first study investigating the effects of UV-B radiation on miRNA expression in mammalian cells was published in 2009 [93]. In this study, the mouse fibroblast cell line NIH3T3 was irradiated with UV-B light and miRNA expression profiling was carried out. UV-B irradiation resulted in robust changes in miRNA expression, in particular 4 h after irradiation, suggesting a role for miRNAs in the early UV response. Among the up-regulated miRNAs was let-7a, a miRNA known to regulate cell proliferation, miR-24, known to be involved in cell cycle regulation and miR-21, a miRNA also up-regulated in several cancer types and in inflammation. The upregulation of miR-21 together with miR-24 has been shown to inhibit cell growth; thus the G1 arrest observed after UV irradiation may in part be mediated by concordant upregulation of these miRNAs.

In line with these results, UV-C irradiation induced extensive changes in miRNA expression in HeLa cells as well as in fibroblasts, with most pronounced changes after 4 h and up-regulation of most miRNAs [94,95]. Although some miRNAs were found to be regulated in both studies (e.g. miR-21, miR-24), many miRNAs are not overlapping and may reflect a difference between the effects of UV-B and UV-C. Interestingly, in cancers and after exposure to carcinogens a general down-regulation of miRNAs is observed; this suggests that the carcinogenic effect of UV may not be directly mediated by miRNA regulation.

The effect of UV-A and UV-B irradiation on the expression of 4 miRNAs in primary human keratinocytes has been recently investigated [96]. UV-A irradiation had a more pronounced effect compared with UV-B; while UV-A induced miR-21, miR-203 and miR-205, UV-B slightly induced miR-203, reduced miR-205 and had no effect on miR-21. In line with this, we observed that only few miRNAs were regulated in three-dimensional epidermal equivalents irradiated with UV-B light (unpublished observations). The effect of UV-B irradiation on miRNAs seems thus to vary dependant on either cell type or time after irradiation.

Does UV-induced miRNA regulation contribute to the cellular and molecular responses to UV irradiation? When silencing Dicer and Ago2, essential components in the miRNA processing pathway, cell survival after UV-C-induced damage in HeLa cells was reduced [94,95], suggesting that miRNAs are involved in UV-induced apoptosis and cell cycle arrest. UV irradiation triggered the relocalization of Ago2 into stress granules, a phenomenon also observed previously in response to other stress stimuli; however, the potential role of this process in UV-induced cellular responses is as yet unclear. The specific miRNAs involved in the UV-induced stress response also remain to be identified. It seems that the effects of UV light on miRNA expression can only partially be generalized to other cell/tissue types, and the effects may differ in a tissue composed of many different cell types such as skin.

5. Conclusions

MiRNAs are the most abundant regulators of gene expression in our genome and they have an enormous regulatory potential. It is now well established that these small noncoding RNA molecules regulate essential biological processes and that their expression is frequently deregulated in diseased tissues. It has also been shown that modulation of miRNA activity can result in favorable therapeutic response in animal models of diseases. The forthcoming years will answer the question whether therapeutic modulation of miRNA activity can have beneficial effects for the patients suffering in chronic inflammatory diseases.

Several studies showed that toxins and pollutants such as cigarette smoke, chemicals, particulate matter as well as UV radiation regulate miRNA expression. Investigation of the role of miRNAs in the cellular response to environmental stimuli is still in its infancy. However, given the important role of miRNAs in cancer

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and inflammation, it is plausible that miRNAs are involved in the proinflammatory and carcinogenic effects of these environmental stimuli. Future studies will be needed to explore whether the observed changes in miRNA expression are indeed linked to a functional response.

Surprisingly, intact, mature miRNAs circulate in plasma and serum and their levels change in disease states. One may hypothesize that altered miRNA levels may be detected in plasma/serum of patients suffering from inflammatory diseases or individuals exposed to toxins and pollutants thus providing a novel class of useful biomarkers.

Conflict of interests

The authors declare no competing financial interests.

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