Spotlight on microRNAs in allergy and asthma

Julie Weidner[1], Sabine Bartel[2], Ayse Kilic[3], Ulrich Zissler[4], Harald Renz[5], Jürgen Schwarze[6], Carsten Schmidt-Weber[7], Tania Maes[8], Ana Rebane[9], Susanne Krauss-Etschmann[10], and Madeleine Rådinger[11]

[1]University of Gothenburg, Institute of Medicine
[2]Universitair Medisch Centrum Groningen
[3]Brigham and Women's Hospital
[4]ZAUM – Center for Allergy and Environment
[5]Philipps University
[6]University of Edinburgh, Edinburgh
[7]ZAUM – Center for Allergy and Environment
[8]Ghent University
[9]University of Tartu
[10]Forschungszentrum Borstel Leibniz-Zentrum fur Medizin und Biowissenschaften
[11]University of Gothenburg

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Abstract

In past ten years, microRNAs (miRNAs) have gained scientific attention due to their importance in the pathophysiology of allergic diseases and their potential as biomarkers in liquid biopsies. They act as master post-transcriptional regulators that control most cellular processes. As one miRNA can target several mRNAs, often within the same pathway, dysregulated expression of miRNAs may alter particular cellular responses and contribute or lead to the development of various diseases. In this review, we give an overview of the current research on miRNAs in allergic diseases, including atopic dermatitis, allergic rhinitis and asthma. Specifically, we discuss how individual miRNAs function in the regulation of immune responses in epithelial cells and specialized immune cells in response to different environmental factors and respiratory viruses. In addition, we review insights obtained from experiments with murine models of allergic airway and skin inflammation and offer an overview of studies focusing on miRNA discovery using profiling techniques and bioinformatic modelling of the network effect of multiple miRNAs. In conclusion, we highlight the importance of research into miRNA function in allergy and asthma to improve our knowledge of the molecular mechanisms involved in the pathogenesis of this heterogeneous group of diseases.

Introduction

The human body is constantly subjected to an onslaught of allergens and environmental irritants. These particles can trigger immune and inflammatory responses leading to a variety of alterations in gene expression. In recent years, the study of non-coding RNAs has led to an increased understanding that gene regulation is more complex than previously imagined[1,2]. Among other mechanisms, small non-coding microRNAs (miRNAs) have found themselves in the role of central regulators of gene expression at the post-transcriptional level. The details of miRNA molecular function, biogenesis and processing have been thoroughly described in several reviews[1-4]. In canonical miRNA processing, miRNAs are transcribed by RNA polymerase II as a pri-miRNA which is then processed by the enzymes DROSHA and DCGR8 in the nucleus to form a pre-miRNA. This pre-miRNA hairpin is exported to the cytoplasm where is it cleaved by DICER into a

miRNA duplex. One of the two strands is loaded into AGO2, whereas the other is degraded. It should be highlighted that miRNAs often initiate the downregulation of their target genes via imperfect binding to the 3' untranslated regions of mRNAs. This imperfect binding leads to the suppression of multiple targets by one miRNA, while a single mRNA can be influenced by several miRNAs. There are several points to take into account when understanding miRNA nomenclature[5]. 1.) Novel miRNAs are named sequentially although there are exceptions for "historical" miRNAs such as let-7 and lin-4 which were first discovered in *C. elegans* . Currently, over 2500 miRNAs have been verified. 2.) miRNA clusters are areas where two or more miRNAs are transcribed from adjacent miRNA genes (e.g. miR17˜92). 3.) miRNA strands are named -5p or -3p indicating if they originate from the 5' or 3' arm and either may be responsible for regulating cellular processes. Nowadays technological advances such as real-time PCR, microarray and next generation sequencing have greatly simplified the identification and validation of miRNAs, allowing for the exponential growth of investigation of miRNAs as regulatory molecules in a wide variety of research areas.

Although miRNAs were first discovered nearly thirty years ago, their detailed role in the immune system has only begun to be elucidated in the past decade. While more thoroughly studied in cancer, recent research has reported miRNA expression to be altered in skin conditions and a variety of lung diseases, including, but not limited to: idiopathic pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, and asthma[6-10]. The use of model systems, such as cell culture and mouse models, have furthered our knowledge of the mechanistic role of miRNAs in airway hyper-reactivity, allergy and immune responses[2,4,11-13]. Research into the role of miRNAs in allergy is expanding and many potential players have been identified in mouse models or *in vitro* studies, but their real role in human disease still remains poorly understood.

This review highlights the recent steps towards a better understanding of the role of miRNAs in allergic diseases including atopic dermatitis (AD), allergic rhinitis (AR) and asthma. Currently, sufficient evidence exists for miRNA regulation in the pathogeneses of these three allergic diseases, but, there is increasing evidence for a role of miRNAs in other allergic diseases such as food allergy or chronic rhinosinusitis[4,10,13-29].**Figure 1** provides an overview of miRNAs in cells and tissues that are associated with allergic diseases.

Human Disease

Atopic dermatitis

AD is a complex chronic inflammatory skin disease that is associated with skin barrier defects and the activation of immune responses in the skin by environmental allergens and/or intrinsic factors.[30] Although type 2 inflammatory responses and elevated IgE are known as the main characteristics of AD, some patients actually develop stronger T helper cell (Th) Th17/Th22 responses[31]. Among other characteristic features, activation of keratinocytes with some similarities to another inflammatory skin disease, psoriasis, plays an important role in AD[30,32]. Research on miRNAs in AD started with an array analysis of lesional skin samples from AD and psoriasis patients. The results of this early study suggested that alterations in miRNA levels in the skin of AD patients partially overlapped with that of psoriatic skin and include multiple miRNAs shown to be modulated in other inflammatory conditions[33]. For example, miR-21 and miR-146a were shown to be upregulated in the skin of psoriasis and AD patients[33], of which miR-21 function in airway inflammation is discussed in other sections of this review. miR-146a was demonstrated to inhibit many pro-inflammatory chemokines in keratinocytes through targeting multiple factors of the NFϰ-B pathway[34-37] and miR-146a-deficient mice developed stronger inflammation in both AD and psoriasis models[36,38]. On the other hand, it has been shown that miR-146a deficiency in mice leads to a defect in IgE production[39,40]and is linked to a type 1/type 17 skewing phenotype[41]. However, as a negative relationship between miR-146a and IgE levels in patient serum samples was detected[39]. It appears that miR-146a is needed for the production of IgE and suppression of type 1/17-cell-mediated immune responses in mice. Therefore, the increased expression of miR-146a in the case of allergic inflammation might have limited influence on type-2 cell-mediated immune responses in a subgroup of AD patients with increased IgE.

Another miRNA that may influence the development of AD through its function in the immune system is miR-155. It was shown that miR-155 is overexpressed in the skin of AD patients, most likely due to

infiltrating immune cells, and suggested that miR-155 may influence the development of AD through the downregulation of cytotoxic T lymphocyte-associated antigen 4 (CTLA4), a negative regulator of T cell activation[37]. In addition, it was reported that miR-155 expression positively correlated with AD severity, the number of Th17 cells and IL-17 mRNA expression and plasma concentration, indicating that miR-155 may influence the pathogenesis of AD through its effect on differentiation and function of Th17 cells[42]. The expression changes and effects in cell cultures of other miRNAs, including miR-151a[43], -143, -124 and 10a are reported and outlined in **Table 1** . Altogether, the studies of miRNAs in AD clearly demonstrate that miRNAs affect the severity of skin inflammation, modulate cellular responses of keratinocytes and specialized immune cells and thereby influence the pathogenesis of AD.

Allergic rhinitis

AR also known as hay fever, represents the most common allergic disease and is characterized by increased circulating IgE levels and/or positive skin prick test. This is triggered by various environmental allergens including pollen, molds, house dust mite and animal dander, and results in a cascade of type 2 immune response in which type 2 cytokine production and eosinophil numbers are increased . AR manifests in the upper airways and often coexists with asthma[44]. Indeed, an estimated 10-40% of AR patients suffer from asthma[45]. Mucosal inflammation in AR and asthma shares many features, which has led to the "united airway concept"[46] and the idea that inflammation in AR can progressively extend to the lower airways[47]. Even though AR and asthma often co-exist, many studies examining AR subjects aimed to uncover unique AR-specific miRNA signatures (**Table 2**). Indeed, a subset of circulating miRNAs in plasma, miR-206, -338-3p, -329 and -26a, were found to be differentially expressed in patients with AR, but not in healthy individuals or those with non-allergic asthma. Random forest model prediction suggested that a subset of six miRNAs allowed for high accuracy in distinguishing between these three groups[48].

In nasal biopsies, out-off-season AR patients displayed higher miR-7 and miRPlus-E1194 expression, whereas let-7, miR-498,-187, -874, -143, -886, -224, and -767 were decreased compared to non-allergic patients undergoing inferior turbinate surgery[49,50]. The reduced levels of let-7e were confirmed by an additional study, which also showed increased levels of miR-155, a miRNA involved in type 2 immune responses (see above[51,52]), miR-205 and miR-498 in nasal biopsies of patients with current AR symptoms[50]. miR-498 was also increased in the nasal mucosa of subjects suffering from perennial allergy, while miR-18a expression was significantly lower in subjects with perennial allergy compared to subjects with sensitization to seasonal allergens[48].

The correlation of miRNAs with AR symptom severity (Total Nasal Symptoms Score) revealed 3 down-regulated (miR-572, -1228-, -483) and 9 up-regulated miRNAs in nasal mucosa (miR-1908, -126, -92a, -125a, 19a, 26a, 106a, -181c, -3177). Of the identified miRNAs, miR-126, -19a and -26a specifically and sensitively predicted AR disease activity in a receiver operating characteristic (ROC) analysis[53], thus suggesting that miRNAs may be potential biomarkers in the prognosis of AR.

Asthma

Asthma is a heterogeneous, chronic disease of the airways associated with airway hyper-reactivity, bronchoconstriction, cough, wheeze and, in the majority of cases, inflammation. The most common and well-studied form of asthma is the allergic type affecting both children and adults. Allergic asthma is marked by increased circulating IgE levels and/or positive skin prick test and triggered by various allergens from pollen and mold to animal dander in addition to airway hyperreactivity. This allergen trigger leads to a cascading type 2 immune response in which type 2 cytokine production, eosinophil numbers and IgE levels are all increased. Given the vast heterogeneity of asthma sub-phenotypes, this section will focus primarily on findings regarding the role of miRNAs in allergic asthma (**Table 3**).

Allergic asthma often begins in early life with up to half of adults reporting asthma symptoms beginning in childhood[54]. Thus, several studies examined the composition of miRNAs in the circulation and their potential as biomarkers. For example, 122 circulating miRNAs differentiated asthmatic from non-asthmatic children[55]. The comprehensive inclusion of phenotypic characteristics in the Childhood Asthma Management Program (CAMP) studies allowed the identification of miRNAs that could potentially aid in the treatment

of childhood asthma[56-58]. These miRNAs correlated to lung function parameters after stratification by sex (miR-126, -139, -15b, -186, -342, -374a, -409, -660, -942, male associated and miR-126, -1290, -142, 191, female associated) and to bronchial hyperresponsiveness in response to methacholine challenge (miR-296, -16 and -30d). Applying machine learning to miRNA expression and the clinical score of asthma from the CAMP cohort, these studies suggested a combination of miRNAs as asthma prediction markers (miR-146b, miR-206 and miR-720)[58].

In adult asthma, a study identified a set of plasma miRNAs, miR-125b, miR-16, miR-299-, miR-206 and miR-133b, that distinguished asthmatics from healthy individuals and subjects with AR[14]. let-7a, miR-21, -133a, -155, -328, and -1248 were all found significantly decreased in exhaled breath condensates from asthmatic individuals compared to healthy subjects and predicted target mRNAs indicated numerous type 2 mediators, suggesting a role for these miRNAs in asthma[15]. miR-21 has been commonly found to be dysregulated in allergic asthma, both in the circulation and in the airways of humans and mice[8-10]. miRNA expression was also shown to be altered in a temporal manner. When allergic asthmatics were examined in and out of the pollen season, miR-155 was found to be downregulated in lymphocytes from induced sputum only in pollen season, raising the question of which other miRNAs may be altered upon pollen exposure [16]. Another prevalent miRNA in asthma, miR-19a has been shown to be a player in asthmatic airways[57,59,60]. Increased expression of miR-19a in airway T cells promoted type 2 cytokine production through direct targeting of Phosphatase and Tensin Homolog (PTEN) and A20, whereas reduced miR-19a in the airway smooth muscle cells led to enhanced remodeling[57,59]. In a recent study, decreased epithelial and sputum miR-221 were associated with eosinophilic airway inflammation in asthma[61]. Even out of the airways, miRNAs have shown potential as predictive markers in asthma. miRNAs from circulating eosinophils, a hallmark in asthma and allergic disease, were examined with miR-185 distinguishing between healthy and asthmatic subjects and showing to be a predictor of asthma severity in blood sera[62].

Numerous biomarker studies have been conducted to find both extracellular vesicle derived miRNAs from bronchoalveolar lavage (BAL) and cell-specific miRNAs dysregulated in asthma[63-65]. Recently more detailed studies have identified potential miRNA targets, suggesting that these aberrant miRNAs alter multiple signaling processes. A negative correlation between lung function parameters and miR-16 in asthma was recently identified. *In silico* analysis predicted Adrenoreceptor B-2 (ADRB2), which is involved in bronchial smooth muscle contraction, as a target gene for miR-16 and was later confirmed by luciferase assay[66]. Bioinformatic analysis of miRNA targets from the blood of house dust mite allergic asthmatic children revealed enrichment in the PI3K and NF-ϰB pathways. More specifically, correlations were shown between their target miRNAs and 3 genes: the E3 ubiquitin ligase CBL, PPARGC1B, which stimulates the activity of various transcription factors and nuclear receptors, and the estrogen receptor ESR1, suggesting that these pathways and genes have a role in asthma pathogenesis[67]. Additionally, miRNA expression in asthma has been correlated to expression and/or targeting of the type 2 cytokines[59,68], IL-13 [69]and IL-5[70], as well as VEGF[71], key molecules in asthma pathogenesis, strengthening the evidence for their role in the regulation of the disease. Now that the field has a large set of potential miRNAs that are shown to be altered in asthma, it is important for more mechanistic studies to be performed to truly understand their role in asthma pathogenesis.

Environmental Factors

miRNAs in the regulation of virus-induced asthma exacerbation

Viruses affecting the respiratory system, such as human rhinoviruses (RVs), respiratory syncytial virus (RSV) and influenza, are known to cause serious illness and exacerbation in asthma patients[72-74]. When infecting human bronchial epithelial cells (HBECs), these viruses activate the NF-ϰB pathway and interferon signaling in order to induce cellular responses, restrict virus replication and avoid tissue damage. It has been suggested that HBECs of asthmatic patients might have weakened interferon responses, resulting in increased viral propagation, enhanced activation of NF-ϰB and immune responses and asthma exacerbations[75]. In this context, it can be envisioned that miRNAs targeting the NF-ϰB pathway and influencing interferon singnaling may have great potential to modulate cellular responses to respiratory viruses and influence the exacerbation

of asthma. Accordingly, one of the earliest studies addressing the question of miRNA involvement in the regulation of viral responses showed an increase in viral replication of RV-1B in HBECs when DICER was knocked down and, additionally, miR-128 and -155 were inhibited[76]. Another study found that miR-18a, -27a, -128 and -155 were downregulated in asthmatic HBECs and that simultaneous knockdown of these four miRNAs led to a significant increase in IL-8 and IL-6 expression[77]. Differences in the bronchial epithelium of asthmatic patients may also occur due to epigenetic changes[78]. miRNAs can influence genes involved in epigenetic regulation or modification and may also influence cellular responses to respiratory viruses. Indeed, a recent study demonstrated the upregulation of miR-22 and downregulation of its target genes histone deacetylase (HDAC)4 and CD147 in response to influenza A virus H1N1 in bronchial epithelial cells from healthy subjects. However, cells from asthmatic patients were incapable of upregulating miR-22 and showed increased and unchanged levels of HDAC4 and CD147, respectively[79]. Several additional studies suggest important functions for miRNAs in the regulation of cellular and immune responses to respiratory viruses (**Table 4**). One example are three miRNAs from different families (miR-24, -124a, -744) that all interfere with the p38 MAPK pathway, through the downstream kinases MK2 and Myc. MK2 and Myc are essential pro-viral host factors and their downregulation by these miRNAs (or small interfering RNA (siRNAs)) confers broad-spectrum antiviral activity against influenza A virus, RSV and adenovirus[80]. Most studies, however, are performed in immortalized bronchial epithelial cells and rarely utilize primary respiratory epithelial cultures, clinical samples or *in vivo* mouse models. Thus, information about the real role of miRNAs in respiratory viral infections and virus-induced asthma exacerbations remains very limited.

The role of air pollution in miRNA regulation

In addition to viral infections, air pollution and cigarette smoke exposure are important contributors to asthma development and/or exacerbations[81-89]. Air pollution is not only associated with aggravated type 2 responses, but can also lead to elevated neutrophil levels which are also a source of miRNAs [90]. Since exposure to air pollution alters miRNA expression both in the lungs and in blood (reviewed in[91]), this could represent an important immunomodulatory mechanism in asthma. However, studies that investigate miRNA expression and function in association with air pollution and allergy or asthma are scarce (**Table 5).**In bronchial brushings from atopic individuals exposed to diesel exhaust and allergen, miR-183, -324 and -132- expression was modulated by allergen exposure, but not by diesel exhaust[92]. Diesel exhaust exposure on the other hand increased expression of miR-21, -30e, -215 and -144 in blood of mild asthmatics. Importantly, miR-21 and miR-144 expression was associated with increased oxidative stress markers and reduced antioxidant gene expression[93]. In Chinese children, increased miR-155 in the serum of asthmatic children correlated with particulate matter level exposure[94]. Indirect exposure by maternal smoking reduced miR-199a expression in cord blood. Interestingly, miR-199a targets the receptor tyrosine kinase AXL, which is more methylated upon maternal smoking and the combination of maternal smoking and AXL methylation modifies the risk of childhood bronchitis symptoms[95]. Tobacco smoke exposure is also associated with increased miR-223 expression in maternal and cord blood and with low numbers of regulatory T cells, which could be important in asthma development[96]. This miRNA was also identified in induced sputum of patients with severe asthma (both atopic and non-atopic) and was associated with increased neutrophils[97]. In lung tissue of murine models with *in utero* smoke exposure combined with allergen challenge, the expression of miR-221, -16, -155, -21- and -18a was increased, whereas miR-130a expression was reduced compared to lungs challenged with allergen only[98,99]. Similarly, 133 microRNAs were dysregulated in fetal murine lungs upon maternal smoking. Bioinformatic network analyses that included microRNAs and transcriptional regulators revealed insulin-like growth factor (Igf-1) as major hub. Dysregulation of IgF-1 was confirmed in PBMCs of healthy school-aged children with early-life smoke exposure[100]. Expression analysis and functional experiments in epithelial cells (primary and cell lines) exposed to air pollution have revealed miRNA involvement in several processes that can be important in asthma, such as oxidative stress, apoptosis, autophagy, NF-$\varkappa$B signaling and epithelial to mesenchymal transition (**Figure 2**)[101-113]. miRNAs reported to be involved in chronic obstructive pulmonary disease (reviewed in [114-116]) may also be important in asthma aggravated by air pollution. Although the actual involvement of these miRNAs in asthma remains to be further investigated, they could become interesting tools for exposure and risk assessment.

Mechanistic Studies

The availability of miRNA -mimics, -inhibitors and -knock out (KO) murine lines in particular have helped to delineate the impact of deregulated miRNA expression on disease pathology and revealed intricate interactions of altered miRNA-regulation (**Table 6**).

miRNAs in innate immune responses in allergic airway inflammation

The exposure to allergens, e.g. house dust mite (HDM), is an important trigger for changes in lung-specific miRNA expression. Allergen contact triggers epithelial release of IL-33, which in turn tightly controls the activation and proliferation of innate lymphoid type 2 cells (ILC2). ILC2s provide early release of type 2 -promoting IL-5 and IL-13 and initiate allergic airway inflammation. Studies in miRNA-KO mice revealed the importance of miRNAs in these early pathogenetic events. Mice deficient in miR-155 exposed to allergen had reduced levels of IL-33 in the airways post allergen challenge and lower ILC2 numbers compared to wild-type mice, revealing a critical role in inducing ILC2 proliferation[117]. In dendritic cells (DC), lack of miR-155 led to reduced chemotaxis and type 2-priming capacity, resulting in ameliorated hallmarks of experimental asthma[41,118,119 120]. A similar phenotype was observed for ILC2s recovered from miR17˜92 cluster deficient mice. These cells were found to be defective in growth and cytokine expression in response to IL-33 and thymic stromal lymphopoietin (TSLP)[121]. However, further studies revealed the complexity within miRNA-clusters, showing that individual family members can have opposing roles. For example, within the miR-17˜92 cluster, the family member mir-19a was found to be elevated in allergic inflammation and shown to promote IL-5 and IL-13 production by targeting the known inhibitors SocS1 and A20[121]. In contrast, miR-19b was downregulated in allergic inflammation and shown to target Tslp. Treatment with miR-19b was able to reduce allergic inflammation, providing evidence for a suppressive role and limiting type 2-inflammation[122]. Another miRNA induced in the murine airway upon allergen contact and Toll-like receptor (TLR) signalling was miR-126. Inhibition of miR-126 using antagomirs was sufficient to suppress the inflammatory response, implicating a prominent role in driving type 2 inflammation[123,124]. The inflammatory milieu in the lung induced the expression of miR-21 in cells of the monocyte/macrophage lineage and structural cells. miR-21 targets IL-12p35 mRNA and thereby critically controls the type 1/ type 2 balance in type 2-high (Ovalbumin [OVA], HDM, *Aspergillus fumigatus*) and steroid-insensitive experimental asthma[125-128]. Furthermore, it was shown that inhibition of miR-9 in experimental allergic, steroid resistant asthma models restored the steroid sensitivity via targeting protein phosphatase 2 regulatory subunit B (B56) δ isoform (PPP2R5D)[129]. miR-9 was also increased in the sputum of patients with neutrophilic asthma, which is often associated with steroid resistance. Additionally, miRNAs seem to control macrophage differentiation into their intrinsic subphenotypes. Along this line, miR-511 was increased in alternatively activated macrophages, but decreased in pro-inflammatory macrophages[130]. A similar study identified an upregulation of miR-124 in alternatively activated macrophages[131] and in $CD14^+CD16^+$ monocytes of patients with asthma compared to controls.

miRNAs controlling adaptive immunity in experimental asthma

In vitro studies in $CD4^+$ T cells revealed a dynamic change of miRNA expression upon activation of cells and polarization into specialized $CD4^+$T cell subsets[132]. Some miRNAs involved in controlling the polarization process are encoded in the polycistronic clusters Mirc11 and Mirc22, comprising miRs-23(a/b), -24 and -27(a/b). Bioinformatic analyses revealed several genes in a gene-network upstream of IL-4 to be among the targets for these miRNAs. In an acute model of experimental asthma, mice bearing $CD4^+$T cells deficient in these miRNAs developed an augmented type 2 response, including high type 2-cytokine levels and elevated eosinophil numbers in BAL[11,133]. Conversely, miR-145 expression was found induced in inflamed lungs and seemed to actively promote and sustain the inflammatory process. Indeed, blockade by antagomirs suppressed the production of IL-5 and IL-13 in the lungs and inhibited the inflammatory phenotype to an extent equal to dexamethasone [134].

Once established, the allergic phenotype is thought to stabilize and reinforce itself by IL-13 production in the inflamed environment. Cellular control mechanisms, that restrict IL-13 expression in the airways, seem to be suppressed in allergic airway inflammation and include the involvement of miRNAs. One example is the let-7

family of miRNAs[135], all of which were found to be downregulated in OVA-induced experimental asthma. Exogenous delivery of let-7 limited eosinophil recruitment and histopathological alterations and airway-reactivity to metacholine[135]. Further examples are miR-133a and miR-448-5p, that are both downregulated in OVA-induced asthma lung tissue and directly target the genes IGF-1 receptor (*Igf1r*)[136]and$T\gamma\varphi\beta1$ [137], respectively. Furthermore, overexpression of both miRNAs was able to reduce remodelling associated genes.

Cell-based functional studies

Several studies investigated miRNA-based molecular mechanisms *ex vivo /in vitro* in different cell types involved in asthma pathogenesis[138-143]. miR-155 is one of the most frequently investigated miRNAs in regards to asthma and AD. miR-155 was shown to be induced by hyper-stretch in human bronchial epithelial cells[144] and targets Src homology 2 domain–containing inositol 5-phosphatase 1 (SHIP1) production and activates Janus Kinase (JNK) signaling leading to KC (the functional IL-8 paralog) secretion in mouse models. miR-181b was observed to be decreased in bronchial brushings and plasma from patients with asthma and inversely correlated with eosinophil counts in sputum[145]. Overexpressing this miRNA in a bronchial epithelial cell line (BEAS-2B) confirmed the regulation of the target Secreted Phospho Protein 1 (SPP1) and reduced IL-13 induced secretion of IL-1β and CC-Motif Chemokine Ligand 11 (CCL11). In this line, miR-181b was induced following addition of dexamethasone. Further, miR-27b has been described to be decreased in HDM induced experimental asthma, with a proposed function in the regulation of the PI3K-AKT pathway via targeting Spleen Associated Tyrosine Kinase (SYK) and Epidermal Growth Factor Receptor (EGFR) in a bronchial epithelial cell line (16-HBE)[55].The let-7 miRNA family is also very abundant in the lung and their inhibition*in vivo* ameliorated murine experimental asthma[69]; in particular, let-7a was shown to regulate IL-13 expression[135] *in vitro* . In concordance to its effect in skin keratinocytes,[35,36]miR-146a was shown to have anti-inflammatory function in human lung alveolar epithelial cell line A549[146,147]and in HBECs.[148]

Besides epithelial cells, several studies have investigated miRNA-regulated mechanisms in airway smooth muscle cells. *In vitro* stimulation of hASMCs with a cytokine cocktail (IL-1β, TNF-α, IFN-γ) caused an increase in miR-146a with the observed effect being stronger in cells from asthmatic donors compared to healthy controls[149]. As inhibition of miR-146a increases cyclooxygenase-2 (COX-2) levels and IL-1β secretion by hASMCs, the authors suggested that miR-146a may be an interesting anti-inflammatory factor in asthma. In line with this study, upregulation of miR-145 in hASMCs was demonstrated upon cytokine stimulation and was associated with enhanced migration and proliferation*in vitro* [150]. Inhibition of miR-145 reversed this effect through the reduced expression of collagen type I and contractile protein MHC via targeting of Krüppel-like factor 4 (KLF-4). Finally, miR-21 was shown to modulate hASMCs proliferation *in vitro* , via targeting PTEN, as identified by lentiviral overexpression experiments[151]. miR-21 has been previously associated with asthma development, mainly due its targeting of i.e. IL-12p35[125,152], highlighting the multi-functional roles of miRNAs in several cell types contributing synergistically to asthma pathology.

miRNA effects in gene networks

miRNA expression analyses from isolated cells, as well as in tissues from disease models, revealed simultaneously altered expression for several miRNAs. This implicates several parallel regulatory events which are not captured by traditional miRNA-single target gene identification methodologies. Recently, network methods have been utilized to assess the outcome of miRNA-regulation from a global perspective, revealing possible relationships between the miRNA-targets and the affected pathways. An example is the generation of a comprehensive regulatory miRNA-mRNA network of *in vitro* differentiated type 2 and Th17 cells compared to naive $CD4^+$ T cells. It identified a strong involvement of the miR-106a˜363 cluster in Th17 differentiation, with decreases particularly of miR-106a, miR-18b and miR-363 in Th17 cells[153]. Conversely, overexpression of the aforementioned miRNAs led to decreased expression of their confirmed target genes *Nuclear Factor of Activated T cells (Nfat5*), *RAR related Orphan Receptor C (Rorc),* and*Rora* ; leading to decreased Th17 differentiation and IL-17 secretion and identifying this miRNA cluster as a potential target for Th17-mediated inflammation. Th17 cell differentiation is also controlled by the miR-17˜92 cluster, in particular by miR-18a[154], which targets Smad4, hypoxia-inducible factor 1a (Hif1a), and Rora. Thus, miR-18a deficiency enhances Th17 differentiation *in vitro* and increases Th17 cells in tissue in experimental asthma

models *in vivo* .

Another approach identified a distinct miRNA-expression pattern in tissue resident type 2 cells in experimental allergic asthma. $CD4^+$ type 2 cells displayed a strong downregulation of miRNAs compared to naïve $CD4^+$ T cells[155] and the expression pattern changed with the transition from acute to chronic airway inflammation. Integrating gene- and miRNA-expression using a network approach, revealed distinct disease stage specific gene-miRNA networks[155]. Pathogenic type 2 responses resulted from combined and cumulative activities of miRNAs, integrating the net effect of induced miR-27b and miR-23b, targeting immune regulatory Tgfb1 and Egfr pathways on the one hand. On the other side, silenced miRNA activity (miR-206, miR-106b and miR-203), allowed the expression of genes involved in immune activation. Antagonizing the *ex vivo* miRNA-expression levels using miRNA-inhibitors and mimics suppressed IL-13 expression in Th2 cells.

Conclusion

miRNA research, thus far, has led to a breadth of information and long lists of potentially interesting miRNAs, but mechanistic studies of miRNA targeting and function are only beginning to emerge. Furthermore, it is unlikely that one miRNA alone holds the key to explain the pathology of asthma or allergic diseases, as it is not possible to outline a single trigger. More likely, there are numerous players and complex networks of interactions that lead not only to disease pathogenesis, but also to heterogeneity, making mechanistic insight into the roles of miRNAs all the more important going forward. We propose that understanding common triggers for changes in miRNA expression in distinct cell populations, at defined disease stages and in specific phenotypes, together with assessing the net effects of miRNAs will help to decipher the pathophysiological consequences of altered miRNA expression in allergic diseases. Nonetheless, we have provided important evidence highlighting a crucial role of miRNA in the pathogenesis of asthma and allergic disease, making them interesting targets for clinical investigations. Besides therapeutic strategies to target single miRNA[123,124,134,156-158], there is increasing interest in using miRNA profiles as biomarkers for (lung) disease[48,58,62,159-163], which we will address in detail in a future review.

Word count: 4694 including headers (without abstract)

Figure legends

Figure 1: Overview of miRNAs discussed in this review

miRNAs are important regulators in allergic diseases. Herein we provide an overview of the miRNAs described within the review and the cell types or organ systems where evidence of their actions have been reported. All miRNAs have been examined in human cells unless indicated in *bold italics* (mouse studies) or *underlined italics* (human and mouse).

Figure 2: The effect of air pollution on miRNA networks and pathways in airway epithelial cells.

Shown is a detailed schematic of miRNA action including known targets.Increased miRNA expression is indicated with upward red arrow, decreased miRNA expression is indicated with downward blue arrow. Black arrows indicate a stimulatory effect on expression or process, black line ending with perpendicular line indicate inhibitory effect. Based on references 66-101.

Table 1. The functions of miRNAs in atopic dermatitis

miRNA	Function
miR-21	Upregulated in AD
miR-146a	Upregulated in the skin and keratinocytes of AD patients; alleviates chronic inflammation in a mouse mode
miR-155	May influence the development of AD by downregulating CTLA-4 in T cells and by modulation of the deve
miR-151a	Altered in the blood plasma of AD patients, may contribute to Th2 skewing and pathogenesis of AD
miRNA-143	May reduce the influence of IL-13 on epidermal keratinocytes
miR-124	Suggested to decrease inflammation in chronic AD skin lesions
miR-223	Upregulated in whole blood of AD patients

miRNA	Function
miR-10a	Upregulated in AD skin, inhibits keratinocyte proliferation

#N.D. – Not determined in publications cited in the current table, may be described by other studies.

Table 2: miRNAs in allergic rhinitis

miRNA	Function
let-7	**Major regulatory mechanism for modulation IL-13 secretion and thereby type-2 inflammation**
miR-206	**Regulator of the VEGF pathway**
miR-338-3p	**Ινηιβιτορ οφ Ωντ/β-χατενιν σιγναλινγ ανδ ινδυχερ οφ επιτηελιαλ-μεσενχηψμαλ τρανσιτ**
miR-329	**Unknown**
miR-26a	**μοδυλατιον οφ ΤΓΦ-β-δεπενδεντ σιγναλλινγ πατηωαψς ανδ ρεπρεσσιον οφ ινφλαμματορ**
miR-7	**Unknown**
miR-498	**Suppressing Th17 cell differentiation via STAT3**
miR-187	**Regulation of T cell response via CD276**
miR-143	**Regulates memory T cell differentiation**
miR-886	**Regulates TGF pathway via SMAD3**
miR-224	**Regulates TGF pathway via SMAD4**
miR-155 [51,52,170,171]	**Important role in host defense, modulates IL-13 pathway in macrophages determining the M2**
miR-205	**Activation of ERK17 pathway**
miR-572	**Regulates type-1 cytokine expression**
miR-1228	**Regulates type 2 responses**
miR-483	**Ινηιβιτιον οφ ΤΓΦβ1**
miR-1908	**Ινηιβιτιον οφ ΤΓΦβ1**
MMP2	[53]
miR-126	**Counter-regulation of IL4 effect**
miR-92a	**Regulation of IL4 effect**
miR-125a	**Dampens down TLR pathway via IL10, suppresses A20**
miR-19a	**Αχτιατες ΤΓΦβ σιγναλινγ**
miR-106a	**Regulation of authophagic activity**
miR-181c	**Down-regulates Osteopontin, modulating TGF**
miR18a	**Regulating TGF pathway**

Table 3. miRNAs in asthma – studies using patient samples and cell cultures

miRNA	Function or findings	Targets#	References
miR-15b, 126, -139,-142, -186,-191, -342, -374a, -409, -660, -942, -1290	Circulating miRNAs (blood) correlating to lung function parameters in children	N.D.	[56]
miR-16, -30d, -296	Circulating miRNAs (blood) correlating to bronchial hyperresponsiveness	N.D.	[57]

miRNA	Function or findings	Targets#	References
miR-146a, -206, -720	Circulating miRNAs (blood) used in combination as potential asthma prediction markers	N.D.	[58]
miR-16, -125b, -133b, -206, -299	Plasma miRNAs able to distinguish asthmatics from healthy individuals or those with allergic rhinitis	N.D	[48]
let-7a, miR-21, -133a, -155, -328, -1248	Decreased in exhaled breath condensates from asthmatic compared to healthy subjects	N.D	[68]
miR-21	Dysregulated in circulation and lungs in allergic experimental murine models and human allergic asthmatics,	N.D	[9-11]
miR-155	Downregulated in the lymphocytes of allergic asthmatics during pollen season	N.D	[172]
miR-19a	Increased in airway T cells Reduction in smooth muscle cells leads to enhanced remodeling	PTEN, A20	[57,59]
miR-221	Decreased levels in epithelial and sputum was associated with eosinophilic airway inflammation in asthma	N.D.	[61]
miR-185	Identified in circulating eosinophils as a distinguisher between healthy and asthmatic subjects. A potential predictor of asthma severity in blood sera.	N.D.	[62]
miR-16	Negatively correlates to lung function parameters	ADRB2	[66]

miRNA	Function or findings	Targets[#]	References
miR-223, -513a and -625	Downregulated in the blood of dust mite allergic asthmatics compared to healthy individuals	CBL, PPARGC1B, ESR1	[55]
let-7a	Abundant in the lungs and regulates IL-13 expression	IL-13	[69]
miR-1248	Interacts with the 3'UTR to promote IL-5 expression	IL-5	[70]
miR-15a	Low levels in CD4+ T cells in pediatric asthma subject	VEGF	[71]
miR-146a	Downregulated in bronchial brushing samples of asthma patients, inhibits IL-8 and CXCL1 expression and neutrophil migration	IRAK1	[148]

[#]N.D. – not determined in publications cited in the current table, may be described by other studies

Table 4. miRNAs and respiratory viruses

miRNA	Function	Targets	References
miR-155	Inhibition results in increased replication of RV-1B in HBECs Overrepresented in extracellular vesicles of children with RV infection	SOCS1 SHIP-1	[76,80]
miR-22	May influence cellular responses to influenza A virus H1N1 in asthmatic HBECs	HDAC4, CD147 (?)	[79]
miR-155,-27a, -18a, -128	Altered in asthmatic HBECs, simultaneous knockdown results in increased IL-8 and IL-6 Alter viral responses in bronchial epithelial cell line	multiple	[76]

miRNA	Function	Targets	References
miRNA-4776	Downregulation of the NF-ϰB inhibitor beta, increased Influenza A virus survival in HBECs	NFKBIB	[173]
miR-221	Downregulated in response to RSV, inhibits viral replication and infectivity	NGF, TrKA	[174]
miR-23b	Downregulates very low density lipoprotein receptor and thereby inhibits infection by minor group of RVs	VLDLR, LRP5	[175]
miR-136	Increased in A549 human lung epithelial cells infected with H5N1 influenza A virus, upregulates IFN-β	RIG-I	[176]
miR-29	Induced in A549 cells by influenza A and PBMCs in influenza patients, induces COX2 and IFN-λ	DNMT3A	[177]
miR-29c	Induced by influenza in A549 cells, may contribute to virus-mediated apoptosis, inhibits innate immune responses	BCL2L2	[178,179]
miR-let-7c	Upregulated in influenza infected A549 cells, may reduce virus replication.	viral M1	[180]
miR-449b	Upregulated in influenza infected A549 cells, regulates antiviral cytokine signaling	HDAC1	[181]
miR-3145	May inhibit influenza A viruses replication	viral PB1	[182]
miR-485	Prevents spurious activation of antiviral signalling, restricts influenza virus H5N1 infection	RIG-I, viral PB1	[183]

miRNA	Function	Targets	References
miR-144	Attenuates the host response to influenza virus by targeting the TRAF6-IRF7 signalling axis in HBECs	TRAF6	[184]
miR-324-5p	Downregulated in A549 cells in response to infection with RNA viruses, enhanced type I and III interferons and interferon-inducible genes	CUEDC2	[185]
miR-24 miR-124a miR-744	Suppress influenza A (all) and RSV (miR-124a, miR-744) infection in A549 cells by inhibition of p38 MAPK expression and activation of MK2	P38MAPK MK2	[63]

Table 5. miRNA studies investigating the relation between pollution and allergy or asthma

miRNA	Function or findings	References
Human data		
miR-183 miR-324 miR-132	In controlled exposures in atopic subjects (exposure chamber) , the miRNA expression was modulated by allergen exposure, but not additionally by diesel exposure	[92]
miR-21 (up) miR-30e (up) miR-215 (up) miR-144 (up)	In controlled exposures in asthma patients (exposure chamber), diesel exposure was associated with increased expression of miR-21, miR-30e, miR-215 and miR-144. miR-144 and miR-21 associated with systemic oxidative stress markers and negative correlation between miR-144 and antioxidant genes	[93]

miRNA	Function or findings	References
miR-199a1 (down)	miR-199a controls AXL (receptor kinase of the TAM (TYRO3, AXL, MERTK) family. Maternal smoking is associated with increased methylation of AXL and with reduced expression of miR-199a. Combination of material smoking and increased AXL methylation alters the risk of childhood bronchitis symptoms.	[95].
miR-223 (up)	Prenatal tobacco exposure is associated with high miR-223 expression in cord and maternal blood with low Treg numbers	[96]
Murine data		
miR-221 (up) miR-16 (up) miR-130 (down)	In a model cigarette-aggravated allergic asthma (in utero side stream cigarette smoke, followed by *Aspergillus fumigatus* exposure), the altered miRNAs are associated with apoptosis and anti-angiogenesis pathways	[98]
miR-155 (up) miR-21 (up) miR-18 (up)	In a model cigarette-aggravated allergic asthma (in utero side stream cigarette smoke, followed by *Aspergillus fumigatus* exposure), these miRNAs are positively associated with Type2 cytokines in bronchoalveolar lavage fluid	[99]

Table 6. miRNAs and mouse models

miRNA	Function	Target	References
miR-21	Induced by Th2 cytokines in DC and macrophages and promotes type 2-driven inflammation.	IL-12p35	[125-128]
miR-126	Induced in airway wall and promotes type 2 inflammation.	TOM1	[123,124]
let-7a-e	Downregulated in CD4+ T cells and suppresses type 2 inflammation.	IL-13	[135]

miRNA	Function	Target	References
miR- 145	Induced by allergen exposure and promotes type 2 inflammation.		[134]
miR-155	Induced in ILC2 in type 2 inflamed airways and neutralization ameliorates experimental asthma phenotype. Involved in Th2 mediated airway inflammation.	S1pr1 PU.1(?)	[41,117-120]
miR-23˜27	Type 2 cells lacking this miR-cluster express elevated type 2 cytokines.	Gene network regulating IL-4	[11,133]
miR17-92	Mice deficient in this miR-cluster develop an augmented experimental asthma phenotype.		[121]
miR-19a	Upregulated in asthmatic airways and promotes experimental asthma.	SOCS1/ A20	[59]
miR-19b	Downregulated in asthmatic airways. Exogenous delivery of miR-19b mimics ameliorate experimental asthma.	TSLP	[122]
miR network miR-27b (up) miR-206 (down) miR-106b (down) miR-203 (down) miR-23b (up)	A miR-network is induced in lung resident type 2 cells and comprises a combination of induced miRs-27b and -23b as well as silenced miR-206, miR106b and miR-203. Antagonism of expression levels reduces type 2 cytokine expression.	Fine tuning of multiple pathways, that suppress inhibitory signals and allow activation and survival of type 2 cells	[155]

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Fig 1

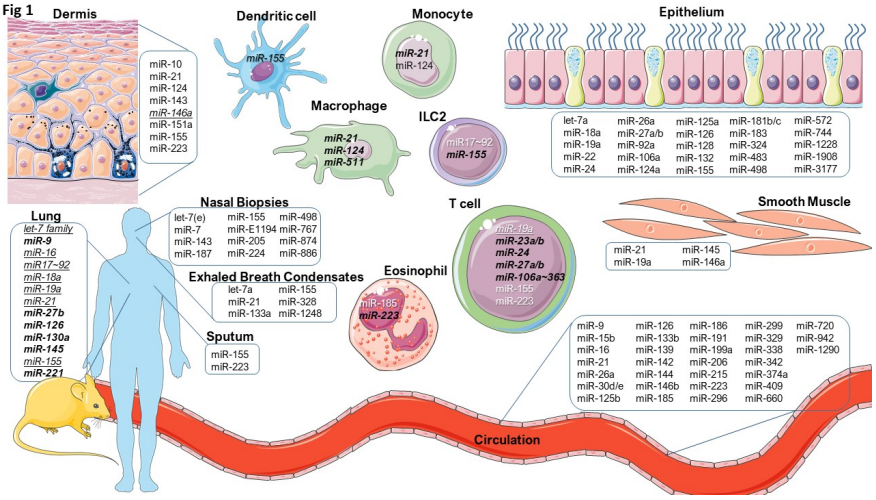

Fig 2