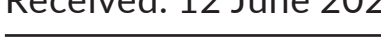

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REVIEW ARTICLE

Spotlight on microRNAs in allergy and asthma

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Abstract

In past 10 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 modeling 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.

KEYWORDS

allergic disease, asthma, experimental models, microRNA, pollution

This review is an output from the EAACI task force "microRNAs in allergy and asthma."

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1 | 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 post-transcriptional gene expression. The details of miRNA molecular function, biogenesis, and processing have been thoroughly described in several reviews[1-4] and presented briefly in Figure 1. It should be highlighted that in mammalian cells miRNAs often initiate mRNA deadenylation followed by degradation 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] (a) Novel miRNAs are named sequentially and currently over 2500 are verified. There are naming exceptions for "historical" miRNAs such as let-7 and lin-4 which were first discovered in *C. elegans*. (b) miRNA clusters are areas where two or more miRNAs are transcribed from adjacent miRNA genes (eg, miR17~92). (c) miRNA strands are named -5p or -3p indicating if they originate from the 5′ or 3′ arm of the hairpin and either may be responsible for regulating cellular processes (Figure 1). Nowadays, technological advances such as real-time PCR, microarray, and next-generation sequencing have simplified the identification and validation of miRNAs, allowing for the exponential growth of investigation of miRNAs as regulatory molecules in numerous 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 alterations in miRNA expression 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 experimental

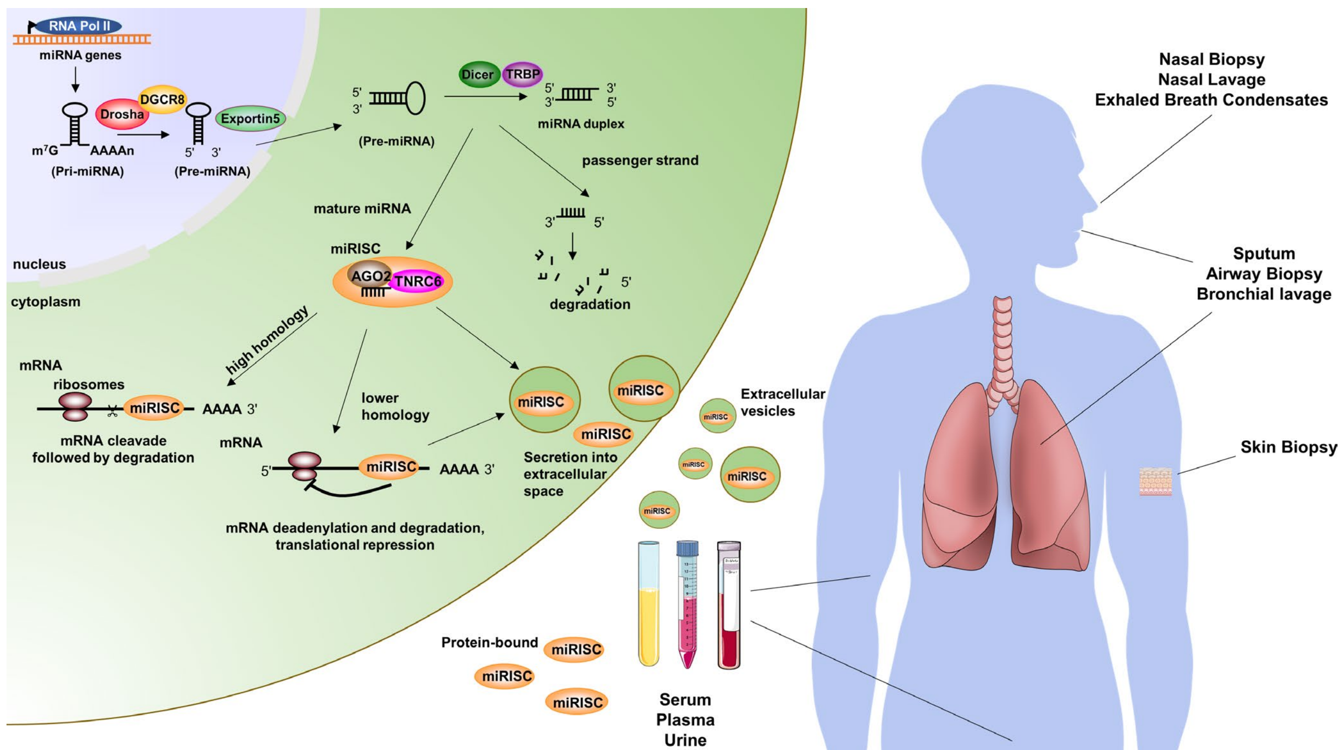

FIGURE 1 microRNA biogenesis and clinical sampling. (Left) miRNAs are transcribed in the nucleus by RNA polymerase II (RNA pol II) and processed by the enzymes Drosha and DiGeorge syndrome critical region 8 (DGCR8) from Pri- to Pre-miRNA. Exportin5 acts to export Pre-miRNAs to the cytoplasm where Dicer and the Dicer binding protein TRBP cut the hairpin to shorter duplexes. While the mature miRNA is incorporated into the miRNA induced silencing complex (miRISC) containing Ago2 and trinucleotide repeat-containing gene 6 (TNRC6) proteins, the passenger strand is degraded. In the miRISC, the mature miRNA acts as a guide RNA for RISC proteins, of which Ago2 has the capacity to cleave mRNA if there is very high homology between the miRNA and the mRNA. If the homology is low, TNRC6 activity predominantly leads to deadenylation and degradation or translational repression of the target mRNA. In addition, miRNAs can be incorporated into different types of secretory vesicles and exit to the extracellular space. (Right) miRNAs are found in cells, tissues and fluids throughout the body. In lung diseases, miRNA levels in fluids, for example serum, plasma and urine (either protein-bound, ie, free, or within extracellular vesicles), are often altered compared to healthy controls. This qualifies them to be used as non-invasive biomarker for lung diseases. Other examples of clinical sampling that would allow for the identification of miRNAs in asthma, atopic dermatitis and allergic rhinitis are illustrated

systems, such as cell culture and mouse models, has 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 laboratory studies, but their actual role in human disease remains poorly understood.

This review highlights the recent steps toward a better understanding of the role of miRNAs in allergic diseases including atopic dermatitis (AD), allergic rhinitis (AR) and asthma. The importance of miRNA regulation in the pathogenesis of the aforementioned allergic diseases is supported by many studies, but also in other allergic diseases such as food allergy or chronic rhinosinusitis the evidence for a role of miRNAs is emerging.[4,10,13-29] Figure 2 provides an overview of miRNAs in cells and tissues that are associated with allergic diseases presented herein.

2 | HUMAN DISEASE

2.1 | Atopic dermatitis

AD is a complex chronic inflammatory skin disease that is associated with skin barrier defects and 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 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, representing, another inflammatory skin disease. 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 included 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] miR-146a was demonstrated to inhibit many pro-inflammatory chemokines in keratinocytes through targeting multiple factors of the NF-κB pathway[34-37] and miR-146a-deficient mice developed stronger inflammation in both AD and psoriasis models.[36,38] It has been shown that miR-146a deficiency in mice leads to a defect in IgE production[39,40] and is linked to a Th1/Th17 skewing phenotype,[41] suggesting that miR-146a is needed for the production of IgE and suppression of Th1/17-cell-mediated immune responses in mice. However, a negative relationship between miR-146a and IgE levels was observed in serum samples from patients.[39] 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, likely due

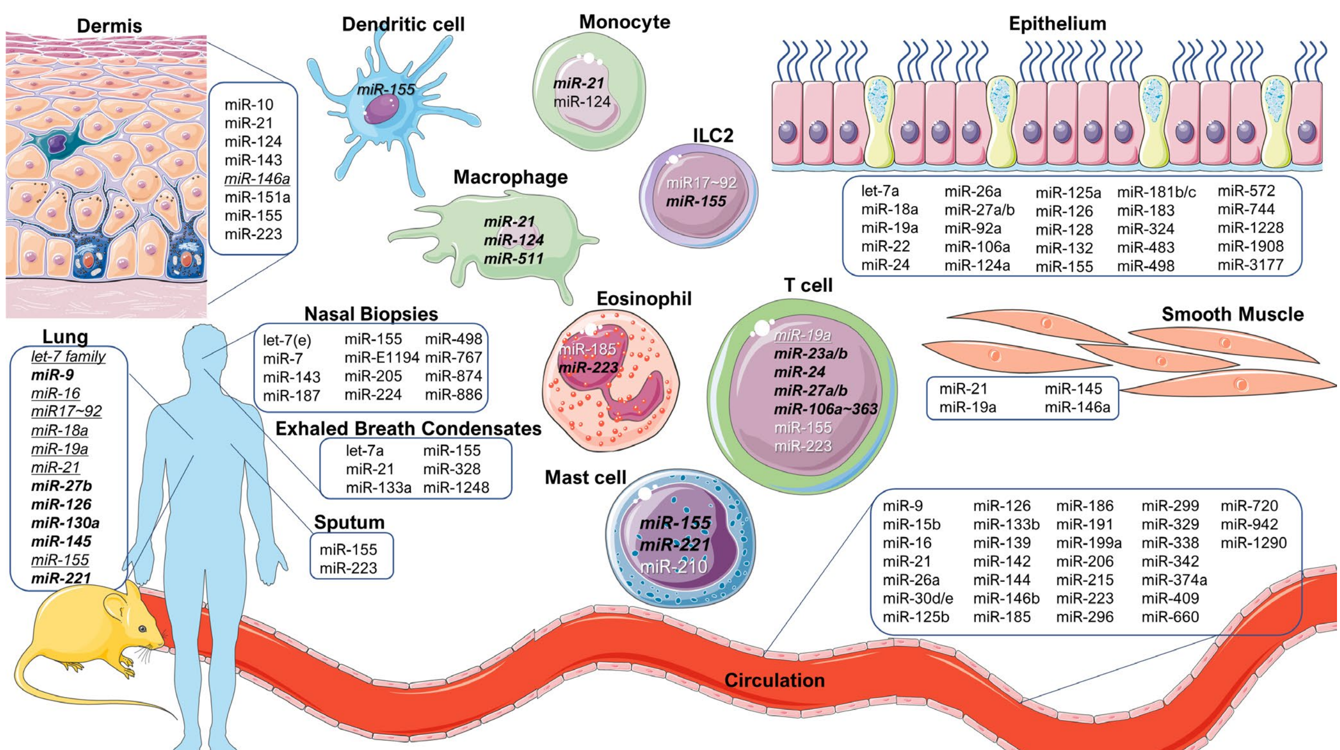

FIGURE 2 Overview of miRNAs discussed in this review. miRNAs are important regulators in allergic diseases. Herein, we provide an overview of the miRNAs described within the review and the cell types or organ systems where evidence of their actions has been reported. All miRNAs have been examined in human cells unless indicated in ***bold italics*** (mouse studies) or *underlined italics* (human and mouse)

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, miR-155 expression was reported to positively correlate with AD severity, the number of Th17 cells, IL-17 mRNA expression and IL-17 plasma concentration, indicating that miR-155 may influence AD pathogenesis through its effect Th17 cells.[42,43] The expression changes and effects in cell cultures of other miRNAs, including miR-151a, -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.

2.2 | Allergic rhinitis

AR represents the most common allergic disease and is characterized by increased allergic symptoms along with circulating allergen-specific IgE levels and/or positive skin prick test. This is triggered by various environmental allergens including pollen, molds, house dust mite and animal dander, resulting in a cascade of type 2 immune response in which type 2 cytokine production and eosinophil numbers are increased. AR, a condition of the upper airways, often coexists with inflammation of the lower airways.[44,45] 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 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-of-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 responding to seasonal allergens.[48]

The diagnostic power of miRNAs was studied in relation to AR symptom severity (Total Nasal Symptoms Score) using microarray which revealed 3 down-regulated (miR-572, -1228-, -483) as well as 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] particularly when miR-126, -19a, and 26a were used in combination. Taken together, several miRNAs were associated with AR, of which only let-7 and miR-26a were identified in independent studies.

TABLE 1 The functions of miRNAs in atopic dermatitis

miRNA	Function	Targets	References
miR-21	Upregulated in AD	ND	33
miR-146a	Upregulated in the skin and keratinocytes of AD patients; alleviates chronic inflammation in a mouse model of AD	IRAK1, CARD10, CCL5	34-36,38-40,175
miR-155	May influence the development of AD by downregulating CTLA-4 in T cells and by modulation of the development of Th17 cells	CTLA-4, SOCS1	37,42
miR-151a	Altered in the blood plasma of AD patients, may contribute to Th2 skewing and pathogenesis of AD	IL12RB2	176
miRNA-143	May reduce the influence of IL-13 on epidermal keratinocytes	IL-13Rα1	177
miR-124	Suggested to decrease inflammation in chronic AD skin lesions	p65	178
miR-223	Upregulated in whole blood of AD patients	ND	148
miR-10a	Upregulated in AD skin, inhibits keratinocyte proliferation	MAP3K7, HAS3	179

Note: ND—not determined in publications cited in the current table, may be described by other studies.

TABLE 2 miRNAs in allergic rhinitis

miRNA	Function	Targets	Citations
let-7	Major regulatory mechanism for modulation IL-13 secretion and thereby type-2 inflammation	JAK1/STAT3, IL-13, SOCS4	50,140,180
miR-206	Regulator of the VEGF pathway	S100A7A VEGF	48
miR-338-3p	Inhibitor of Wnt/β-catenin signaling and inducer of epithelial-mesenchymal transition	WNT/ β -Catenin	48
miR-329	Unknown	TGF-β1	48
miR-26a	Modulation of TGF-β-dependent signaling pathways and repression of inflammatory responses by promoting regulatory T-cell responses or through NF-κB inhibition	SMAD2, SMAD3	48
miR-7	Unknown	CMKLR1	49
miR-498	Suppressing Th17 cell differentiation via STAT3	STAT3	48,50
miR-187	Regulation of T-cell response via CD276	CD276	49,50
miR-143	Regulates memory T-cell differentiation	TGF-β1	49,50
miR-886	Regulates TGF pathway via SMAD3	SMAD3, FoxO1	49,50
miR-224	Regulates TGF pathway via SMAD4	SMAD4	49,50
miR-155	Important role in host defense, modulates IL-13 pathway in macrophages determining the M2 phenotype	IL13Ra1	51,52,181,182
miR-205	Activation of ERK17 pathway	MICAL2	50
miR-572	Regulates type-1 cytokine expression	SOCS1	53
miR-1228	Regulates type 2 responses	PPAR	53
miR-483	Inhibition of TGFβ1	TGFβ1	53
miR-1908	Inhibition of TGFβ1	SMAD2, SMAD3 MMP2	53
miR-126	Counter-regulation of IL4 effect	VEGF, IRS1	53
miR-92a	Regulation of IL4 effect	WNT5a	53
miR-125a	Dampens TLR pathway via IL10, suppresses A20	TLR, A20	53
miR-19a	Activates TGFβ signaling	TGFβ1	53
miR-106a	Regulation of autophagic activity	NOD1/2	53
miR-181c	Down-regulates Osteopontin, modulating TGF	Osteopontin (SPP1)	53
miR18a	Regulating TGF pathway	CTGF	48

2.3 | Asthma

Asthma is a heterogeneous, chronic disease of the lower 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 associated with increased circulating allergen-specific IgE levels and/or positive skin prick test and triggered by various allergens in addition to airway hyper-reactivity. 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 in childhood.[54] 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 for the identification of miRNAs, through microarray analysis, 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,

TABLE 3 miRNAs in asthma—studies using patient samples and cell cultures

miRNA	Function or findings	Targets	Citations
miR-15b, 126, -139,-142, -186,-191, -342, -374a, -409, -660, -942, -1290	Circulating miRNAs (blood) correlating to lung function parameters in children	ND	56
miR-16, -30d, -296	Circulating miRNAs (blood) correlating to bronchial hyper-responsiveness	ND	57
miR-146a, -206, -720	Circulating miRNAs (blood) used in combination as potential asthma prediction markers	ND	58
miR-16, -125b, -133b, -206, -299	Plasma miRNAs able to distinguish asthmatics from healthy individuals or those with allergic rhinitis	ND	48
let-7a, miR-21, -133a, -155, -328, -1248	Decreased in exhaled breath condensates from asthmatic compared to healthy subjects	ND	59
miR-21	Dysregulated in circulation and lungs in allergic experimental murine models and human allergic asthmatics	ND	9-11
miR-155	Downregulated in the lymphocytes of allergic asthmatics during pollen season	ND	60
miR-19a	Increased in airway T cells. Reduction in smooth muscle cells leads to enhanced remodeling	PTEN, A20	57,61
miR-221	Decreased levels in epithelial and sputum was associated with eosinophilic airway inflammation in asthma	ND	64
miR-185	Identified in circulating eosinophils as a distinguisher between healthy and asthmatic subjects. A potential predictor of asthma severity in blood sera	ND	66
miR-16	Negatively correlates to lung function parameters	ADRB2	70
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	72
miR-1248	Interacts with the 3′UTR to promote IL-5 expression	IL-5	73
miR-15a	Low levels in $CD4^+$ T cells in pediatric asthma subject	VEGF	74
miR-146a	Downregulated in bronchial brushing samples of asthma patients, inhibits IL-8 and CXCL1 expression and neutrophil migration	IRAK1	153
miR-210	Increases in human mast cells following IgE sensitization	ND	183
miR-155, -146a, miR-223, -374a	Serum miRNAs correlating to clinical parameters in asthma subgroups	ND	65

Note: ND—not determined in publications cited in the current table, may be described by other studies

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

Studies in adult asthma have also identified numerous miRNAs that may assist in better identifying and understanding the disease. Significantly decreased expression of let-7a, miR-21, -133a, -155, -328, and -1248 were found in exhaled breath condensates from asthmatic individuals compared to healthy subjects. Furthermore, numerous type 2 mediators were predicted targets of these miRNAs, suggesting their role in asthma.[59] The dysregulation of miR-21 in circulation and the airways has been commonly reported in allergic asthma, and thoroughly studied in humans and mice.[9-11] Certain miRNA expression was shown to be altered in a temporal manner with miR-155 found to be downregulated in sputum lymphocytes from allergic asthmatics only during pollen season.[60] This raises the question as to which other miRNAs may be altered upon pollen exposure. miR-19a, another miRNA often altered in asthma, has multiple roles in the asthmatic airway.[61-63] Increased expression of miR-19a in airway T cells promoted type 2 cytokine production through direct targeting of Phosphatase and Tensin Homolog (*PTEN*) and TNF Alpha Induced Protein 3 (*TNFAIP3*) and reduced miR-19a in the airway smooth muscle cells led to enhanced airway remodeling.[61,63] In a recent study, decreased epithelial and sputum miR-221 were associated with eosinophilic airway inflammation in asthma.[64] Even out of the airways, miRNAs have shown potential as predictive markers in asthma. A study identified a set of plasma miRNAs, miR-125b, -16, -299, -206, and -133b, that distinguished asthmatics from healthy individuals and subjects with AR.[48] Recent studies in blood

serum used miRNAs to identify asthma subgroups[65] and another identified miR-185, a circulating eosinophil derived miRNA, to be a predictor of asthma severity.[66]

Numerous biomarker studies have been conducted to find both extracellular vesicle derived miRNAs from bronchoalveolar lavage (BAL) and cell-specific miRNAs dysregulated in asthma.[67-69] Recently, more detailed studies have identified potential miRNA targets, suggesting that multiple signaling processes may be affected. A negative correlation between lung function parameters and miR-16 in asthma was recently identified.[70] *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.[70] 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 three genes: the Cbl Proto-Oncogene (*CBL*), PPARG Coactivator 1 Beta (*PPARGC1B*) and the estrogen receptor 1 (*ESR1*), suggesting that these pathways and genes have a role in asthma pathogenesis.[71] Additionally, miRNA expression in asthma has been correlated to expression and/or targeting of the type 2 cytokines,[59,61] IL-13 [72] and IL-5,[73] as well as VEGF,[74] key molecules in asthma pathogenesis, strengthening the evidence for their role in the regulation of the disease. Having shown the alteration of a large set of miRNA in asthma calls for further investigation to mechanistically define their role(s) in asthma pathogenesis.

3 | ENVIRONMENTAL FACTORS

3.1 | 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.[75-77] 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.[78] In this context, it can be envisioned that miRNAs targeting the NF-κB pathway and influencing interferon signaling 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.[79] 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.[80] Differences in the bronchial epithelium of asthmatic patients may also occur due to epigenetic changes.[81] 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.[82] Several additional studies suggest important functions for miRNAs in the regulation of cellular and immune responses to respiratory viruses (Table 4). Three miRNAs from different families (miR-24, -124a, -744) all interfere with the p38MAPK 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.[83] Recently more studies have utilized primary respiratory epithelial cultures, including air-liquid interface cultures, clinical samples and in vivo mouse models[84] possibly leading to better clarification of the functions of miRNAs also during respiratory viral infections and virus-induced asthma exacerbations.

3.2 | 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.[85-93] 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.[94] Since exposure to air pollution alters miRNA expression both in the lungs and in blood (reviewed in Ref. 95), 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.[96] 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.[97] Increased miR-155 in the serum of asthmatic children correlated with particulate matter level exposure.[98] 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.[99] 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.[100] This miRNA was also identified in induced sputum of patients with severe asthma (both atopic and non-atopic) and was associated with increased neutrophils.[101]

TABLE 4 miRNAs and respiratory viruses

miRNA	Function	Targets	References
miR-155	Inhibition results in increased replication of RV-1B in HBECs.	ND	79,83
miR-22	May influence cellular responses to influenza A virus H1N1 in asthmatic HBECs	HDAC4, CD147 (?)	82
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	79
miRNA-4776	Downregulation of the NF-κB inhibitor beta, increased. Influenza A virus survival in HBECs	NFKBIB	184
miR-221	Downregulated in response to RSV, inhibits viral replication and infectivity	NGF, TrKA	185
miR-23b	Downregulates very low density lipoprotein receptor and thereby inhibits infection by minor group of RVs	VLDLR, LRP5	186
miR-136	Increased in A549 human lung epithelial cells infected with H5N1 influenza A virus, upregulates IFN-β	RIG-I	187
miR-29	Induced in A549 cells by influenza A and PBMCs in influenza patients, induces COX2 and IFN-λ	DNMT3A	188
miR-29c	Induced by influenza in A549 cells, may contribute to virus-mediated apoptosis, inhibits innate immune responses	BCL2L2	189,190
miR-let-7c	Upregulated in influenza infected A549 cells, may reduce virus replication	viral M1	191
miR-449b	Upregulated in influenza infected A549 cells, regulates antiviral cytokine signaling	HDAC1	192
miR-3145	May inhibit influenza A virus replication	viral PB1	193
miR-485	Prevents spurious activation of antiviral signaling, restricts influenza virus H5N1 infection	RIG-I, viral PB1	194
miR-144	Attenuates the host response to influenza virus by targeting the TRAF6-IRF7 signaling axis	TRAF6	195
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	196
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	83
miR-146a	Increased in response to H3N2, targets TRAF6 in human nasal epithelial cells. Decreases IFN-stimulated gene expression and enhances infection with influenza A virus in A549 cells	TRAF6 TRAF6	197 198
miRNA-126a, miRNA-16 and miRNA-21	Serum levels significantly lower during exacerbation visit as compared to follow-up visit	ND	199

Note: ND—not determined in publications cited in the current table, may be described by other studies.

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.[102,103] Similarly, using miRNA arrays it was demonstrated that 133 miRNAs were dysregulated in fetal murine lungs upon maternal smoking.[104] Subsequent bioinformatic network analyses that included miRNAs and transcriptional regulators revealed insulin-like growth factor (Igf-1) as a major hub. Dysregulation of IgF-1 was confirmed in PBMCs of healthy school-aged children with early-life smoke exposure.[104] In a murine cockroach asthma model, particulate matter exposure led to increased inflammatory responses, which were associated with elevated expression of miR-206. This miRNA targets the antioxidant enzyme superoxide dismutase 1 (*SOD1*) leading to induction of oxidative stress, which may drive the pollution-driven aggravated inflammatory response.[105] 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-κB signaling and epithelial to mesenchymal transition (Figure 3).[106-118] miRNAs reported to be involved in chronic obstructive pulmonary disease (reviewed in Ref. 119-121) may also

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

miRNA	Function or findings	Citations
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	96
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	97
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	99
miR-223 (up)	Prenatal tobacco exposure is associated with high miR-223 expression in cord and maternal blood with low Treg numbers	100
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	102
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	103

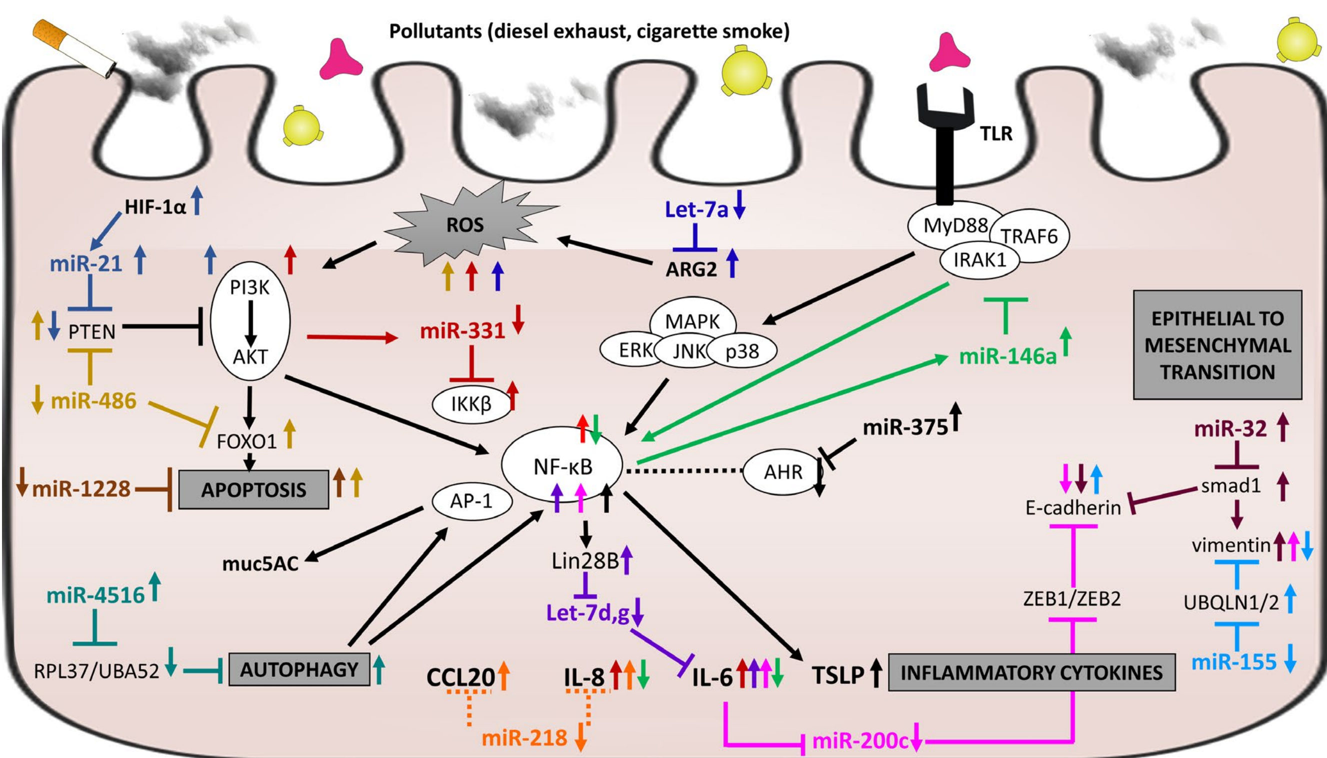

FIGURE 3 The effect of air pollution on miRNA networks and pathways in airway epithelial cells. Shown is a detailed schematic of miRNA action including known targets. Increased miRNA expression is indicated with upward red arrow, and decreased miRNA expression is indicated with downward blue arrow. Black arrows indicate a stimulatory effect on expression or process, and black line ending with perpendicular line indicates inhibitory effect. Smoke, pink and yellow figures represent air pollutants that may affect epithelial cells. Based on references 106-118

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.

4 | MECHANISTIC STUDIES

The availability of miRNA-mimics, -inhibitors, and -knockout (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). Mechanistic studies performed in murine models and human cell culture have broadened our understanding of miRNAs and have paved the way for future translational studies.

4.1 | miRNAs in innate immune responses in allergic airway inflammation

The exposure to allergens, for example, 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 type2-promoting IL-5 and IL-13 and initiate allergic airway inflammation. Studies in miRNA-KO mice revealed the importance of miRNAs in these early pathogeneic 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.[122] In dendritic cells (DC), lack of miR-155 led to reduced chemotaxis and type 2-priming capacity, resulting in ameliorated hallmarks of experimental asthma.[41,123-125] A similar phenotype was observed for ILC2s recovered from miR-17~92 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).[126] 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 *Tnfaip3*.[126] 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.[127] Another miRNA induced in the murine airway upon allergen contact and Toll-like receptor (TLR) signaling 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.[128,129] 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.[130-133] 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*).[134] 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.[135] A similar study identified an upregulation of miR-124 in alternatively activated macrophages[136] and in $CD14^+CD16^+$ monocytes of patients with asthma compared to controls.

4.2 | 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.[137] 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 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.[11,138] 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.[139]

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,[140] 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 methacholine.[140] The let-7 miRNA family is also very abundant in the lung and their inhibition in vivo ameliorated murine experimental asthma.[72] However, in an additional study, let-7a was shown to inhibit IL-13 expression by directly targeting *Il-13*[140] in vitro and exogenous administration of a let-7 microRNA mimic alleviated asthmatic features in a mouse model of asthma. Additional examples that are both downregulated in OVA-induced asthma lung tissue are miR-133a and miR-488 which directly target the genes IGF-1 receptor (*Igf1r*)[141] and *Tgfβ1*,[142] respectively. Furthermore, overexpression of both miRNAs was able to reduce remodeling associated genes.

TABLE 6 miRNAs and mouse models

miRNA	Function	Target	Reference
miR-21	Induced by Th2 cytokines in DC and macrophages and promotes type 2- driven inflammation	IL-12p35	130-133
miR-126	Induced in airway wall and promotes type 2 inflammation	TOM1	128,129
let-7a-e	Downregulated in CD4$^+$ T cells and suppresses type 2 inflammation	IL-13	140
miR- 145	Induced by allergen exposure and promotes type 2 inflammation		139
miR-155	Induced in ILC2 in type 2 inflamed airways and neutralization ameliorates experimental asthma phenotype. Involved in Th2-mediated airway inflammation. Regulates mast cell activity	S1pr1 PU.1(?) PI3Kγ pathway(?)	41,122-125,200
miR-23~27	Type 2 cells lacking this miR-cluster express elevated type 2 cytokines	Gene network regulating IL-4	11,138
miR-17-92	Mice deficient in this miR-cluster develop an augmented experimental asthma phenotype		126
miR-19a	Upregulated in asthmatic airways and promotes experimental asthma	SOCS1/A20	61
miR-19b	Downregulated in asthmatic airways. Exogenous delivery of miR-19b mimics ameliorates experimental asthma	TSLP	127
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	164
miR-1	Downregulated by VEGF. Intranasal miR-1 delivery inhibited inflammatory responses in experimental asthma models	Mpl	201,202
miR-221	Influences effector functions and actin cytoskeleton in mast cells	ND	203

Note: ND—not determined in publications cited in the current table, may be described by other studies.

4.3 | Cell-based functional studies

Several studies investigated miRNA-based molecular mechanisms ex vivo/in vitro in different cell types involved in asthma pathogenesis.[143-148] miR-155 was shown to be induced by hyper-stretch in human bronchial epithelial cells[149] 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 decreased in bronchial brushings and plasma from patients with asthma and inversely correlated with eosinophil counts in sputum.[150] 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] 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[151,152] and in HBECs.[68,153-157] Interestingly, it was recently shown that primary human airway epithelial cells secrete miRNAs in extracellular vesicles (EV)[154] as a means of intercellular communication by functionally transferring miRNAs to recipient cells.[155] The miRNA content of epithelial EVs was altered when the cells were treated with IL-13, suggesting a differential regulation of target genes in recipient cells. Further, EVs isolated from BALF[68] or plasma[156] of patients with asthma contained different miRNAs compared to healthy individuals. This ability of miRNAs to be transferred between different cells adds another layer of complexity to their involvement in perpetuating anasthmatic response in the airways.[157]

Besides epithelial cells, several studies have investigated miRNA-regulated mechanisms in airway smooth muscle cells

(hASMCs). 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 asthmatic donor cells than healthy controls.[158] 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.[159] 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.[160] miR-21 has been previously associated with asthma development, mainly due its targeting of, that is, *IL-12p35*,[130,161] highlighting the multi-functional roles of miRNAs in several cell types contributing synergistically to asthma pathology.

4.4 | 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 affected biological pathways. An example of such comprehensive regulatory miRNA-mRNA networks has been simulated for in vitro differentiated Th17 cells. Compared to naive $CD4^+$ T cells, Th17 cells expressed lower levels of miR-106a, miR-18b and miR-363 all belonging to the miR-106a~363 cluster.[162] 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 *Rorα*; entailing decreased Th17 differentiation and IL-17 secretion, therefore 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,[163] which targets *Smad4*, hypoxia-inducible factor 1α (*Hif1α*), and *Rorα*. 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.[164] Compared to naïve $CD4^+$ T cells, type 2 cells in inflamed lungs displayed a strong downregulation of miRNAs[164] and this 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.[164] Pathogenic type 2 responses were predicted to result from combined and cumulative miRNA activities. Type 2 inflammation was predicted to result from elevated miR-27b and miR-23b, targeting immune regulatory Tgfb1 and Egfr pathways on the one hand and on the other hand, reduced expression of miR-206, miR-106b and miR-203, allowing for the expression of genes involved in immune activation. Antagonizing this ex vivo miRNA-expression pattern in vitro using miRNA-inhibitors and mimics suppressed IL-13 expression in Th2 cells and supported the in silico predictions of an intricate network of miRNA regulation.[164]

Notably, we have mainly discussed the influence of miRNAs in the regulation of the immune response in allergic diseases. However, as individual miRNAs influence a wide range of targets and pathways, it is only logical to assume that several other pathways, such as, for example, metabolic pathways, might be affected at the same time and are also relevant for asthma pathogenesis.

5 | 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. 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 that change 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. As asthma and allergy are very heterogeneous conditions and because current treatments are still inefficient in controlling severe forms of these diseases, more individualized and effective therapies are in a great demand.[165-167] Interest in novel therapeutics strategies to target single miRNAs[128,129,139,168-170] is increasing as well as the interest in using miRNA profiles as biomarkers for (lung) disease.[48,58,65,66,171-174] To implement the use of miRNAs as biomarkers, they should be specific, have the capacity to predict disease phenotypes, and be easily detectable in body fluids. Several studies mentioned in this review (eg, CAMP study) demonstrate that miRNAs indeed have this potential. We will address the challenges and potential pitfalls associated with the use of miRNAs as biomarkers in a future review.

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CONFLICT OF INTEREST

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GLOSSARY

AGO2—a member of the Argonaute family of proteins that plays a central role in RNA silencing through the binding of small RNAs such as miRNAs.

DCGR8—a nuclear protein required for mRNA processing. DCGR8 binds to Drosha and forms a complex that cleaves the primary transcript known as pri-miRNA into a characteristic stem-loop structure known as a pre-miRNA.

Drosha—a nuclear RNase III that cleaves primary miRNAs (pri-miRNAs) to release hairpin-shaped pre-miRNAs.

Dicer—a cytoplasmic RNase III that cuts the pre-miRNA to form mature miRNA.

pre-miRNA hairpin—precursor-miRNAs (*pre-miRNA*) refer to the *hairpin* precursors of miRNAs formed by the cleavage of primary miRNAs by DCGR8 and Drosha.

miRNA duplex—the sense and antisense strand of the pre-miRNA hairpin that is cleaved to a double stranded RNA. One strand will ultimately be degraded.

miRISC—The RNA-induced silencing complex is a ribonucleoprotein complex comprised of proteins such as Dicer, Ago2 and TRBP and miRNA. The miRISC will target an mRNA for post-transcriptional regulation.

Polycistronic clusters—a primary transcript encoding more than one miRNA or mRNA.

Antagomirs—a class of chemically engineered oligonucleotides that are used to silence endogenous miRNA.

Biomarker—A biological molecule found in fluid or tissue that allows for the identification of a specific condition/disease.

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