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Chapter

Pathogenic Roles of MicroRNA in the Development of Asthma

Xiaoyan Dong and Nanbert Zhong

Abstract

Asthma is a common and chronic inflammatory disease. Pathogenic mechanism underlying asthma is complicated. The inflammatory reactions in asthma have been recognized to involve mast cells, eosinophils, lymphocytes (T cells, B cells), macrophages, and dendritic cells. MicroRNA (miRNA, miR) is a group of small noncoding RNAs with 21–25 nucleotides (nt) in length, which impact biologic responses through the regulation of mRNA transcription and/or translation. MicroRNAs are related to developmental processes of many immunologic diseases. Most studies showed that regulation of miRNAs to their targeting genes appears to play an important role in the development of asthma. This chapter has discussed altered expression of miRNAs in cells and tissues from patients with asthma, in order to better understand the mechanics of pathogenesis of asthma. In addition, the regulation of miRNAs as a novel therapeutic approach will require a deeper understanding of their function and mechanism of action.

Keywords: microRNA asthma, inflammation reaction

1. Introduction

Pediatric asthma is a global problem. In the last decade, its incidence has highly increased, particular growing by 10% in China [1]. Etiologically, asthma attack, due to gene-environmental interactions, can also be induced by allergy factors, including air pollution, pollen, fungi and dust mites, food, and so on [2]. As a chronic inflammatory disease and a polygenic hereditary disease, the mechanism of asthma is not clearly understood until now. The adaptive and innate immune system with the involvement of mast cells, eosinophils, lymphocytes (T cells, B cells), macrophages, and dendritic cells, even epithelial cells and structure cells, contributed to the inflammation reaction of asthma [3–5]. Moreover, change in the secretion of IgE and cytokines, including gamma-interferon (γ-IFN) and tumor necrosis factor (TNF-α), is important in asthma attacks [6–8]. As an immune regulator, microRNA (miRNA or miR) regulates on target gene mRNA and plays an important role in the development and pathogenesis of asthma.

MicroRNAs are a group of small nonprotein-coding RNAs that are 21–25 nucleotides in length. They act as transcriptional regulators involved in many complex human disorders and in biological processes including cell proliferation and apoptosis [9, 10]. Childhood asthma susceptibility is associated with mutations in specific gene mRNA and/or their specific miRNA. For example, HLA-G has been identified as an asthma susceptibility gene [11], which was found to be the target gene of miR-148a,

miR-148b, and miR-152. Further support for the theory that miRNA changes may be the cause of childhood asthma. The specific genotype of children with asthma was related to the significant difference in allele polymorphism (SNP) of rs2910164G/C and rs2292832C/T of pre-miRNA [12]. It showed that miR-223 was involved in the maturation and function of neutrophil differentiation [13]. miR-27b-3p, miR-513a-5p, and miR-22-3p were also indicated to have influenced dust mite-induced asthma by regulating its target gene [14, 15]. In a murine model of acute and chronic asthma study, abnormal expression of miRNAs including miR-146b, miR-223, miR-29b, miR-29c, miR-483, miR-5745p, miR-672, and miR-690 in asthma was

miRNA	Inflammatory response	Reaction and cell differentiate	Reference
miRNA-223	Immune inflammatory response	Neutrophils mature and differentiate	[13]
miRNA-146, miRNA-146a	Asthma, innate immune responses	Airway epithelium, NF-kappaB pathway	[17, 18]
miRNA-147	Immune inflammatory response	TLR signaling pathway	[19]
miRNA-145	Asthma	Comparable to glucocorticoid treatment	[20]
miRNA-155	Immune inflammatory response, asthma	TLR signaling pathway, regulation of allergic inflammation, macrophage inflammatory response, Th2 priming of dendritic cells	[21–24]
miRNA-21	Immune inflammatory response, asthma	TLR signaling pathway, NF-kB, IL-12p35 polarization	[25–27]
miRNA-124	Allergy inflammation	M2 phenotype of monocytic cells	[28]
miRNA-148a, miR-148b, and miR-152	Asthma	HLA-G	[11, 29]
miRNA-126	Asthma	Th2 response, airway hyperresponse	[30]
let-7	Asthma	Il-13, regulation of allergic inflammation	[31–33]
miRNA-221	Asthma	Mast cell activity regulates the production of cytokines	[34, 35]
miRNA-9	Asthma	Regulates steroid-resistant airway hyperresponsiveness	[36]
miRNA-672, miRNA-143	Asthma	Expression of metalloproteinase	[37]
miR-19a	Asthma	Enhances proliferation of bronchial epithelial cells by targeting TGFbetaR2 gene	[38]
miRNA-203	Asthma	Negatively regulates c-Abl, ERK1/2 phosphorylation, and proliferation in smooth muscle cells	[39]
miRNA-133, miR-133a	Asthma	Upregulation of Rhoa in bronchial smooth muscle cells	[40]
miR-192	Asthma	Decreased expression in peripheral blood of asthmatic individuals undergoing an allergen inhalation challenge	[41]

Table 1.
The relationship of miRNA and inflammation response.

detected [16]. It was found that miRNA plays an important role in regulating immune pathway(s). A lot of studies have focused on the relationship between miRNA and asthma during decades, which involved not only in inflammation cells and cytokines but also in the treatment of glucocorticoids (**Table 1**). In this chapter, we discuss the relationship of miRNAs to their targeted mRNA(s) involved in the inflammation cell in asthma, in order to review the pathogenic mechanism of asthma.

2. miRNA in T cell and B cell

T cell and B cell play an important role in immune mechanism, especially innate and adaptive immunity, of asthma. As an immune regulator, miRNA influences on these two cells and regulates their proliferation and function. Many studies have been focused on the regulation of miRNA to T cell and B cell in order to clear the mechanism of asthma.

2.1 T cell, follicular helper T cells (TFH cells), and Th17

T follicular helper (Tfh) cells are essential for the formation of germinal centers (GCs). As a subset of CD4+, it mediates GC formation and maintenance and provides help to antigen-specific B cells during infection and vaccination. Th17 cells have also been implicated in the pathogenesis of several autoimmune and inflammatory diseases [42–44]. Th17 cells also mediate immune responses that are involved in maintaining epithelial barrier integrity, and it has been widely suggested that some cases of asthma may be caused by dysregulated Th17 responses [44, 45]. MiRNA also regulates the differentiation and function of these cells.

It was found that the miR-17-92 cluster's increasing role in regulating the immune system is involved in innate and adaptive immunity, including B cells and subsets of T cells such as Th1, Th2, T follicular helper cells, regulatory T cells, monocytes/macrophages, NK cells, and dendritic cells [46]. Moreover, the study found that the miR-17 approximately 92 cluster is a critical regulator of T cell-dependent antibody responses and follicular helper T cells' (TFH cells) differentiation [47].

We knew that the relationship of miRNA and its target gene mRNA is not a one-to-one correspondence. Target gene mRNA could be regulated by many miRNAs, or one miRNA could regulate a number of mRNAs. A study showed that some miRNAs with strong probability may induce miR-27b, miR-27a, miR-30c, miR-1, and miR-141 or inhibit miR-20b, miR-93, miR-20a, miR-152, miR-21, and miR-106a in Th17 differentiation by targeting negative or positive regulators of Th17 differentiation, respectively [48]. In a regulatory network model of murine T helper cell differentiation, the miR-212~132 and miR-182~183 clusters were significantly upregulated, and the overall miR-106~363 cluster was downregulated, which predicted to affect Th17 cell differentiation. In vitro, when miR-18b, miR-106a, and miR-363-3p were transfected into primary murine Cd4(+) lymphocytes, the expression of retinoid-related orphan receptor c (Rorc), Rora, IL17a, and IL17f and abolished secretion of Th17-mediated interleukin-17a (IL17a) have declined [49].

In addition, miR-18a directly targeted Smad4, Hif1a, and Rora in the Th17 cell gene expression program. All of these reveal that activating signals influence the outcome of Th cell differentiation via differential regulation of mature microRNAs within a common cluster [50]. miR-18a was the most dynamically upregulated microRNA of the miR-17-92 cluster during Th17 cell differentiation. Based on which, the involvement of miR-18a in the regulation of T-cell differentiation was demonstrated.

miR-155, as an important regulator in asthma, was involved in many pathways in allergy disease in **Table 1**. It was shown that the function in macrophage

inflammatory response [23] is differentially expressed in allergic T cells exposed to DM extract compared to in nonallergic cells. The level of miR-155 expression was positively associated with the expression of the TH2 cytokines IL-5 and IL-13. When miR-155 was inhibited by glucocorticoids in Jurkat T cells, then the production of these cytokines were inhibited [51].

Several differentially expressed miRNAs in asthma, such as miRNA-34/449, let-7, miRNA-19, miRNA-21, and miRNA-455, were identified in various cell types and tissues including epithelial cells, T cells, type 2 innate lymphoid cells, lung tissues, and smooth muscles. These miRNAs are involved in epithelial differentiation, mucus production, airway remodeling, and inflammation as well [52]. miR-146a has been shown to modulate T-cell immunity as well as enhance class switch and secretion of IgE in B cells by upregulating 14-3-3 sigma expression [53].

2.2 miRNA regulates B cell

B cells play a critical role in immune responses, but the regulation of microRNAs to B-cell proliferation and function was partially understood. Not only miR-17-92 cluster was involved in B cell [46], but miR-146a also enhances class switch and secretion of IgE in B cells [53]. As an important immune regulatory cell, thrombospondin 1 (TSP1)-producing B cells were regulated by miRNAs as well. miR-98 can suppress the expression of TSP1 in the peripheral B cells of patients with allergic asthma [54]. Further study revealed that overexpression of miR-29b in human B cells precipitated a reduction in overall AID protein whose activity affected the function of class-switch recombination (CSR) and then results in corresponding diminution in CSR to IgE [55].

3. miRNA and mast cell

It is essential that mast cells have major effector and immune regulatory functions in IgE-associated allergic diseases or in innate and adaptive immune responses. But their mechanism was not clear yet. miRNAs provide an additional layer in the regulation of gene expression acting as repressors with several targets at the posttranscriptional level. Several studies showed that miRNA expression patterns during differentiation and activation of mast cells. The expression of many miRNAs changes following IgE-FcepsilonRI cross-linking in activated mast cells. Upregulated expression of miR-221 promotes IgE-mediated activation of mast cell degranulation by PI3K/Akt/PLCgamma/Ca^{2+} signaling pathway, in a non-NF-kappaB-dependent manner [56]. Downregulation of miR-223 promotes degranulation *via* the PI3K/Akt pathway by targeting IGF-1R in mast cells [57]. In cockroach allergen model of asthma, when miRNA-33b was overexpressed, mast cell degranulation was inhibited through suppression of the calcium release and IgE-FcepsilonRI pathway [58]. In line with this, neutralization of miR-132 by anti-miR inhibitor leads to sustained production of HB-EGF protein in activated mast cells [59].

Cytokine is also related to miRNA and mast cells in inflammation response of asthma. The treatment of IL-10 has been shown to suppress TNF production in mast cells. IL-10 effects are dependent on Stat3 activation, eliciting miR-155 expression, with a resulting loss of suppressor of cytokine signaling-1 [60]. miR-221, which was overexpressed in a murine asthma model, stimulated IL-4 secretion in mast cells through a pathway involving PTEN, p38, and NF-kappaB [61]. miR-223 reduces IL-6 secretion in mast cells by inhibiting the IGF1R/PI3K signaling pathway [62]. Mex-3B, an antisense oligonucleotide targeting, directly upregulates IL-33 expression by inhibiting miR-487b-3p-mediated repression of IL-33 [63].

4. miRNA and dendritic cells

Dendritic cells (DCs) are the professional antigen-presenting cells (APCs) in the lung. They are found to be crucial in the induction and maintenance of allergic asthma by cross-linking innate and adaptive immune responses. After transfection with miR-23b reagents, DCs were evaluated for endocytic ability, surface marker expression, cytokine secretion, and CD4+ T-cell differentiation. The study proved that miR-23b is capable of inducing tolerogenic DC activity and Treg responses in vitro through the inhibition of the Notch1 and NF-kappaB signaling pathways; thus, miR-23b might represent a therapeutic target for the management of allergic diseases [64].

miR-155 has been shown to be a crucial regulator of the immune system mentioned above. Not only miR-155 can influence on T cell function but also regulate the activity of DCs. Deficiency of miR-155 on DCs was also associated with impaired purinergic receptor signaling and alleviates AAI by diminishing Th2 priming capacity and ATP-/P2R-induced activation of DCs in mice [24].

5. miRNA and inflammatory phenotype (neutrophilic asthma and eosinophilic asthma)

Asthma may be classified according to severity and inflammatory phenotype and is likely to be distinguished by specific microRNA (miRNA) expression profiles. The study of miRNA expression in sputum supernatants with the inflammatory cells in severe asthma was taken out. Expression of miR-629-3p, miR-223-3p, and miR-142-3p was significantly upregulated in the sputum of patients with severe asthma compared with that in healthy control subjects and was highest in patients with neutrophilic asthma. It suggested that these miRNAs are related to asthma inflammatory phenotype [65].

Single-nucleotide polymorphisms (SNPs) in miRNAs could affect their efficiency in binding to messenger RNAs (mRNAs), which was taken little into account before. In a study in Korean population, it showed that the CT/CC genotype of miR-196a2 at locus rs11614913 was associated with eosinophilic asthma and a higher sputum eosinophil count than the TT genotype. The CG/GG genotype at rs2910164 of miR-146a had a hyperresponsiveness in airway compared with the CC genotype. The AG/GG genotype at rs3746444 of miR-499 manifested higher predicted values of forced expiratory volume in 1 s (%FEV1) than the AA genotype [66].

A study about evaluating clinical potential of plasma miR-21 and miR-146a involved in T helper cell differentiation in childhood asthma found that the levels of miR-21 and miR-146a were not only positively correlated with eosinophil percentage but also associated with FEV1. miR-21 and miR-146a are upregulated in asthmatic children. miR-21 and miR-146a play a role in eosinophilic endotypic classification of asthma [67]. Moreover, its data show that miR-185-5p profile in eosinophils can be used as asthma diagnosis biomarker in serum and that this profile is able to rank asthma severity [68].

6. miRNA and macrophage

Monocytes and macrophages are important roles of the immune system, which possess pleiotropic effector and immunoregulatory functions. Classical activation (M1) and alternative activation (M2) of macrophages are necessary in the function. M1 polarization of macrophages results in the production of proinflammatory cytokines and antimicrobial and tumoricidal activity, whereas M2 polarization

of macrophages is related to immunosuppression, tumorigenesis, wound repair, and elimination of parasites [69]. It also reveals that miRNAs were involved in M macrophages' activity. miR-511 is increased in macrophages following IL-4 and IL-13 stimulation and decreased in M1 macrophages both in vitro and in vivo [70]. Particularly, miR-9, miR-127, miR-155, and miR-125b have been shown to promote M1 polarization, while miR-124, miR-223, miR-34a, let-7c, miR-132, miR-146a, and miR-125a-5p may induce M2 polarization in macrophages by targeting various transcription factors and adaptor proteins. Differentiation of monocytes to macrophages is inhibited by miR-24, miR-30b, miR-142-3p, and miR-199a-5p. MiR-155 and miR-142-3p inhibit macrophage proliferation, compared to let-7a. Interestingly, miR-155 has both pro- and antiapoptotic roles, whereas miR-21 and let-7e negatively regulate macrophage apoptosis [69, 71, 72]. These data revealed that the function of miRNAs in modulating macrophage polarization may have potential way in the treatment of inflammation-related diseases.

On the other hand, studying the development of allergy disease in maternal pregnancy revealed that the embryonic development is highly sensitive to xenobiotic toxicity. If exposed to environmental toxins in utero, it affects physiological responses of the progeny. In the animal model, there was a lower expression of miR-130a and increased expression of miR-16 and miR-221 in the lungs of mice which were exposed to sidestream cigarette smoke (SS) or secondhand smoke exhibit. These miRNAs regulate HIF-1 alpha-regulated apoptotic, angiogenic, and immune pathways. This process will lead to increase incidence of allergic asthma (AA) and bronchopulmonary dysplasia (BPD) in the progenies [73].

Besides, the expression of miRNAs was different in fungal bioaerosols which are ubiquitous in the environment, and human exposure can result in a variety of health effects ranging from systemic, subcutaneous, and cutaneous infections to respiratory morbidity including allergy, asthma, and hypersensitivity pneumonitis. It was found that miRNAs were involved in the inflammatory stimuli exposure to fungal. In studies of exposures to fungi (such as *Aspergillus fumigatus*, *Candida albicans*, and *Cryptococcus neoformans*), it was revealed that several miRNAs that were shared between responses to these species including miR-125 a/miR-125 b, miR-132 [43], miR-146a, and miR-29a/miR-29b were also involved in macrophage polarization/activation, TLR-mediated signaling, natural killer cell function, C-leptin signaling, and inhibition of Th1 immune response, respectively [74]. On the other hand, miR-487b can suppress the levels of mRNA and protein for IL-33, which plays an important role in macrophage activation for innate host defense and proinflammatory responses during the differentiation of bone marrow-derived macrophages (BMDMs) [75].

In summary, miRNAs exert their effect by binding to complementary nucleotide sequences of the targeted messenger RNA, thus forming an RNA-induced silencing complex. miRNAs play important roles in many aspects of macrophage biology and thereby affect many biological and pathological conditions, like monocyte differentiation and development, macrophage polarization, infection, tumor growth, inflammatory activation, and so on [71, 72]. Numerous studies have demonstrated the important role of miRNA in the pathogenesis of childhood asthma, suggesting that miRNA plays a regulatory role between genes and the environment as well as allergic airway inflammation. The mechanism of miRNA activity involves a large number of miRNAs, which take mRNA with multiple functions as target genes and synergistically regulate multiple aspects of complex pathophysiological processes in childhood asthma. The role of miRNAs in inflammation cells is important in both innate and acquired immunity in which T cell, B cell, mast cells, macrophages, and dendritic cells are involved. The role of miRNAs in these cell types, miR-17-92 cluster, miR-221, miR-223, miR-146a, and miR-155, may be crucial

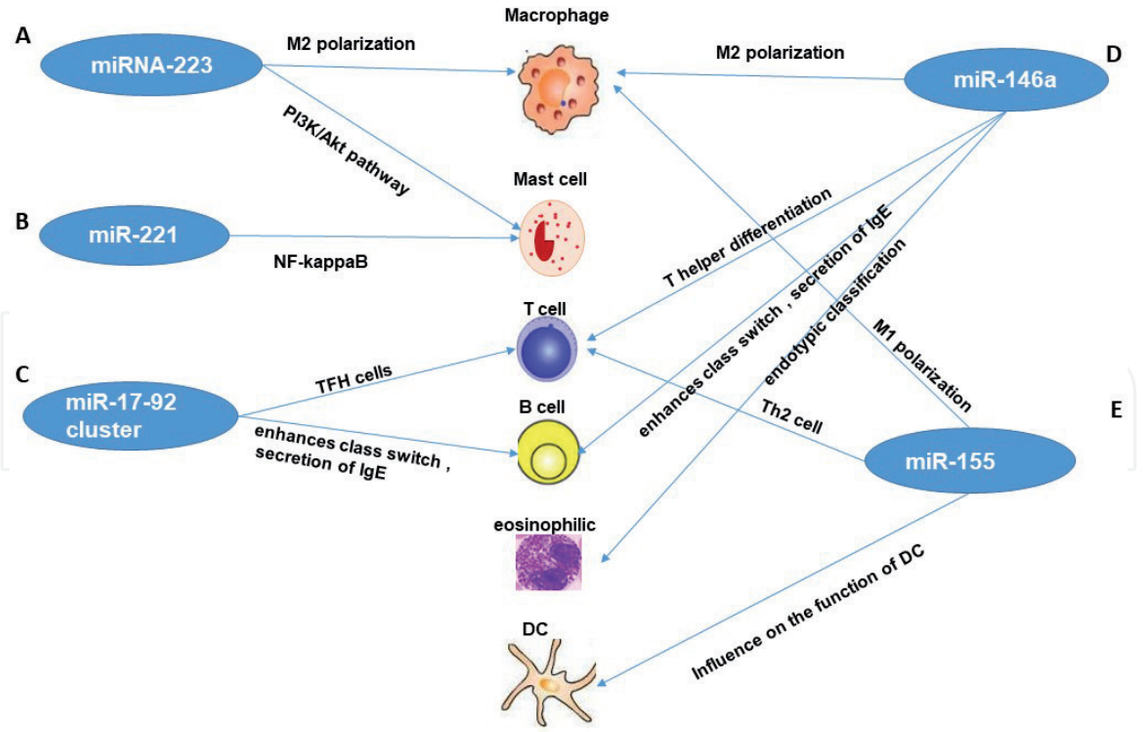


Figure 1.
miR-17-92 cluster, miR-221, miR-223, miR-146a, and miR-155 are associated with inflammation cells. (A) Downregulation of miR-223 promotes degranulation via the PI3K/Akt pathway by targeting IGF-1R and reduces IL-6 secretion in mast cells. It also induced M2 polarization. (B) miR-221 promoted IgE-mediated activation of mast cells degranulation by PI3K/Akt/PLCgamma/Ca^{2+} signaling pathway and stimulated IL-4 secretion in mast cells through a pathway involving PTEN, p38, and NF-kappaB. (C) miR-17~92 cluster as a critical regulator of T-cell-dependent antibody responses and follicular helper T cell (TFH cell) and Th17 differentiation. It enhances class switch and secretion of IgE in B cells. (D) miR-146 modulated T-cell immunity and enhanced class switch and secretion of IgE in B cells. miR-146a played a role in eosinophilic endotypic classification of asthma. It induced M2 polarization as well. (E) miR-155 was associated with Th2 cell and cytokine secretion. Deficiency of miR-155 on DCs was also related to impaired purinergic receptor signaling and alleviates AAI by diminishing Th2 priming capacity and ATP-/P2R-induced activation of DCs. It promoted M1 polarization.

(**Figure 1**). Depending on these roles of miRNAs in dendritic cells, mast cells, and macrophages, we speculate about possible future directions in the field [76]. It is likely variant miRNAs form a network in which these miRNAs may interact with each other and alter the expression of target genes in the inflammation process of pediatric asthma. On the other hand, it is envisaged that targeted manipulation of specific miRNAs could be developed as a new treatment for asthma. At present, our group has already had some result about the relationship of miRNA to target gene in dust mite-induced asthma. Depending on this review, further investigation should be pursued on the immune regulatory function of miRNA in children's asthma.

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Conflict of interest

There was no conflict of interest (economic, personal, scientific, healthcare, educational, religious, and social) interfering with the chapter.

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