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Chapter

Epigenetic Regulation of Th2 Response in Asthma by Non-Coding RNAs

Yanhua Niu, Chao Wang, Xiaoyan Dong and Nanbert Zhong

Abstract

Asthma is a common chronic inflammatory disease. Pathogenic mechanism underlying asthma is complex. The inflammatory response of asthma includes lymphocytes (T, B cells), ILC2, eosinophils and other types of immune and inflammatory cells. T CD4+ T helper 2 cells (Th2 cells) are thought to play a central role in regulating the phenotype of allergic asthma. Asthma is often closely associated with Th1/Th2 cell imbalance. Non-coding RNAs (ncRNAs) are non-protein coding RNA molecules in the transcriptome, mainly including microRNAs (miRNAs), long non-coding RNAs and circRNAs, etc., which are widely found in eukaryotic transcriptome and participate in the regulation of a variety of biological processes. ncRNAs are considered to function as modulators of the immune system. Their biological changes represent an important mechanism for the development of immune-mediated diseases. This chapter mainly discusses the epigenetic regulation of Th2 cells and their cytokines in asthma by non-coding RNAs. It helps us to better understand the pathogenesis of asthma and find potential asthma biomarkers.

Keywords: asthma, Th2, cytokines, non-coding RNAs

1. Introduction

Asthma is a chronic airway inflammatory disease, associated with variable expiratory airflow limitation, clinically manifested as recurrent wheezing, shortness of breath, chest tightness, cough and other symptoms [1]. It has affected more than 300 million people worldwide and has become a major public health concern [2].

Non-coding RNAs (ncRNAs) are a class of non-coding RNA molecules widely found in eukaryotes and involved in a variety of biological regulatory processes. They have been extensively studied in human diseases [3–5]. NcRNAs mainly includes microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), etc.

The pathogenesis of asthma remains extremely complicated and the detailed mechanisms are not clarified. The most common phenotype is eosinophilic inflammation associated with Th2 response and concomitant atopic diseases. Asthma is often closely associated with Th1/Th2 cell imbalance. Th2 cells secrete Th2 cytokines, including interleukin-IL-4, IL-5, and IL-13, which amplify type 2 inflammation, while Th1 cells secrete Th1 cytokines [interferon IFN-γ, IL-2, lymphoid (LT)-α, and tumor necrosis factor TNF-α, which limit type 2 inflammation [6, 7].

The CD^{4+} T cells are major effector cells driving asthma-related inflammation and the skewing of T cells into Th2 cells can lead to imbalance of Th1-type and Th2-type cytokines, which promotes the onset and progression of asthma [8, 9]. Understanding the factors contributing to Th2 in asthma will provide important insights into the underlying pathogenesis of the disease. The skewing of T cells into Th2 cells causes an imbalance of Th1-type and Th2-type cytokines, which promotes the onset and progression of asthma. A number of studies have shown that ncRNAs may play an important role in Th2 cell-mediated inflammation in asthma. This chapter mainly discusses the epigenetic regulation of Th2 response in asthma by non-coding RNAs, in order to better understand the disease pathogenesis and find potential asthma biomarkers.

2. Regulation of microRNAs on Th2 in asthma

MicroRNAs are a group of small nonprotein-coding RNAs that are 18–25 nucleotides in length. They act as transcriptional regulators involved in many complex human disorders and in biological processes including cell proliferation and apoptosis [10–12]. MiRNA expression profiles have also been described in some allergic conditions and asthma [13]. Previous studies have suggested that miRNAs are involved in the development of allergic diseases by affecting Th1/Th2 polarization, promoting chronic inflammation and tissue remodeling of epithelial cells, and activating innate immune cells [13]. Th2-mediated inflammation is the core of the pathogenesis of allergic asthma. Th2-dominated T lymphocytes regulate allergic diseases by secreting a variety of proinflammatory cytokines. Recent studies have shown that most of the miRNAs involved increase Th2 cytokine secretion, reduce Th1 cytokine secretion, promote T cell differentiation to Th2, or play a role in the proliferation and hypertrophy of bronchial smooth muscle cells [14–16]. There is no doubt that miRNA plays a role in the regulation of asthma inflammation. MiRNAs may regulate Th2 in asthma by affecting Th1/Th2 balance, secretion of Th2 cytokines and related signaling pathways.

2.1 Regulation of Th2 cytokines by miRNAs

Th2-mediated inflammation is the core of the pathogenesis of allergic asthma. Typical cytokines involved in the Th2 response are IL-4, IL-5, and IL-13. Pua et al. [15] studied the miRNA related to Th2 cell differentiation and cytokine production by combining experimental and bioinformatics methods, and found that both miR-24 and miR-27 inhibited the production of IL-4 in T cells in vitro. Inhibition of the function of miR-145 suppresses house dust mites (HDM)-induced mucus hypersecretion in airway epithelial cells, eosinophilic inflammation, th2 cytokine production, and airway hyperresponsiveness as effectively as dexamethasone treatment. This study shows that miR-145 plays a key role in the occurrence and pathogenesis of allergic airway disease caused by house dust mites by inducing the release of IL-5 and IL-13 from Th2 cells [14]. Panganiban et al. found a variety of differentially expressed miRNAs in the serum of patients with asthma, and predicted that these miRNAs could regulate IL-5 and other TH2 mediators [17]. It was further confirmed that IL-5 was regulated by miRNA, and miR-1248 was identified as a positive regulator of IL-5 expression [17]. IL-10 levels are reduced in asthmatic patients, and the relative deficiency of IL-10 allows continued production of allergenic cytokines, such as IL-4 and IL-5, and other pro-inflammatory cytokines, including IL-1, TNF-α, and IL-6 [18]. Inhibition of miR-106a promotes IL-10 secretion and helps alleviate asthma symptoms by increasing Th2 response in a mouse

model of asthma [19]. Simpson et al. demonstrated that the miR-17 ~ 92 cluster, and specifically miR-19a, promotes Th2 cytokine production by simultaneously targeting inhibitors of the NF-κB, JAK–STAT, and PI (3)K pathways. Their data also suggest that upregulation of miR-19a in asthma airway T cells may be an indicator and cause of increased IL-13 production and may contribute to type 2 inflammation in asthma [20]. In ovalbumin (OVA)-induced asthma mice, miR-146a significantly inhibited inflammatory cell infiltration in bronchoalveolar lavage fluid (BALF) and reduced levels of OVA-specific IgE and T-helper 2 cell type cytokines (IL-5 and IL-13) [21]. MiR-146a may act as a novel therapeutic molecule to modulate the immune response of asthma. MiR-155 has been shown to be a key modulator of the immune system. MiR-155 may regulate Th2 inflammation by regulating Th2 cell differentiation and the secretion of IL-4, IL-5 and IL-13. These studies suggest that targeting miR-155 may be a novel therapeutic strategy for human diseases induced by the Th2 immune response, such as asthma [22, 23]. It has been found that let-7 microRNAs inhibit IL-13 expression and thereby modulate Th 2 inflammation in an IL-13-dependent mouse model of allergic airway inflammation [24]. In ovalbumin (OVA) -induced asthma mice, intranasal administration of miR-410 significantly reduced the expression of IL-4 and IL-13 and effectively inhibited airway inflammation in OVA-induced asthmatic mice. Therefore, targeting to increase the expression of miR-410 may be a promising approach for the treatment of allergic asthma [25]. In a mouse model of asthma induced by ovalbumin, the researchers tested the airway hyperresponsiveness, rt-pcr detection of miR - 135 a content in the lung tissue of mice, HE staining to evaluate the pathological changes of lung tissue and ELISA and immunohistochemical detection of bronchoalveolar lavage fluid (BALF) and lung tissue of the tumor necrosis factor (TNF) - alpha, interleukin (IL) - 6, IL - 5 and eosinophils chemokine expression. The results of this study showed that miR-135a decreased expression in asthmatic mice, and miR-135a reduced the levels of inflammatory cytokines TNF-α, IL-6, IL-5 and eosinophilic chemokines in the lung tissue of mice, thereby reducing airway inflammation. Further research in this study showed that miR-135a inhibited airway inflammation in asthmatic mice by regulating the JAK/STAT signaling pathway [26]. Previous studies in human, animal models, and cell culture have shown that the Th2 cytokine IL-13 is an important cause of airway epithelial abnormalities in asthma [27–29]. Kuperman et al. used miRNA microarray to analyze the bronchial epithelial cells of asthmatic patients and healthy control subjects, and found that the expression of miR-34/449 family members was decreased in asthmatic patients. IL-13-induced reduction of miR-34/449 in bronchial epithelial cells may lead to changes in epithelial differentiation common in asthma [30]. Zhang et al. investigated the role of miR-221-3p in airway eosinophilic inflammation in a mouse model of HDM-induced allergic airway inflammation, and showed that epithelial miR-221-3p expression was reduced in asthma. Airway overexpression of miR-221-3p induced the expression of IL-4, IL-5, and IL-13 mRNAs in the lungs of mice induced by HDM [31]. The expression of miR-26a, miR-146a, and miR-31 and cytokine levels of IL-5, IL-8, IL-12, and TNF-α were measured in lung tissue and bronchoalveolar lavage fluid of asthmatic mice and children with ovalbumin induced asthma. The results showed that miR-26a, miR-146a, and miR-31 were significantly elevated in asthma, and were involved in the progression of asthma by regulating the expression of inflammatory cytokines IL-5, IL-8, IL-12, and TNF-α [32]. The systems immunology approach (the Impact of Differential Expression Across Layers, a network-based algorithm to prioritize disease-relevant miRs based on the central role of their targets in the molecular interactome) was used to antagonize miRs (miR27b, miR206, miR106b, miR203, and miR23b) in vitro, which has significantly reduced cytokine production in Th2 cells. These results suggest that these miRNAs play an important role in the

Th2-driven immune response [33]. In conclusion, many miRNAs play an important role in asthma by regulating the secretion of Th2 cytokines. They may be new targets for the treatment of asthma in the future.

2.2 Regulation of Th1/Th2 balance by miRNAs

Qui et al. detected the levels of Th1- and Th2-related cytokines by ELISA, performed microRNA microarray assay and analyzed the differentiation marker gene of T helper cells by qRT-PCR. The results indicated that an imbalance of Th1/Th2 cells was present in the asthmatic patients; Runx3 expression is decreased in asthmatic patients; overexpression of Runx3 could restore the Th1/Th2 balance; miR-371, miR-138, miR-544, miR-145, and miR-214 could directly bind to the 3'-UTR of Runx3. All these findings suggest that these miRNAs may be involved in Th1/Th2 imbalance in asthma by regulating Runx3 [34]. One study used predictive algorithms dentified potential direct miR-21 targets among IL-13-regulated lung transcripts such as IL-12p35 mRNA that was decreased in IL-13 transgenic mice. MiR-21 was significantly elevated in ovalbumin-induced mice lungs, suggesting that miR-21 regulates Th1 to Th2 phenotypic transformation by decreasing the mouse IL-12p35 transcriptome [16]. Reduced levels of miR-29b were found in the lungs and spleens of OVA-induced asthmatic mice, and this miRNA indirectly affects the Th2 response by regulating the production of T-box transcription factors and IFN-γ in T helper cells [35]. Low expression of miR-29b in asthmatic lung can increase the production of IFN-γ and restore the balance of Th1/Th2 in asthmatic lung [36]. The researchers evaluated the relationship between miRNA levels in small extracellular vesicles (sEVs) from nasal washing and pulmonary function parameters in children with mild to moderate or severe asthma compared to healthy controls. The results showed that lower levels of miR-34a, miR-92b and miR-210 in children with sEVs in this study were associated with pulmonary function and airway obstruction. Subsequent functional pathway analysis showed reduced levels of miR-92b, miR-210, and miR-34a in epithelial-derived sEVs in asthma, and these miRNAs regulate Th2 polarization and dendritic cell maturation [37].

2.3 miRNAs regulation of Th2 differentiation via signaling pathways

Inhibition of microRNA-126 (miR-126) has been shown to effectively inhibit Th2-driven airway inflammation, mucus hypersecretion, and airway hyperresponsiveness in a model of ovalbumin (OVA) -induced chronic asthma [38]. The blocking of miR-126 leads to the enhanced expression of POU domain 2 related factor 1, which activates the transcription factor PU1, that changes the function of Th2 cells by negatively regulating the expression of GATA3 [39]. In childhood asthma, miRNA-451a was found to inhibit Th2 cell differentiation by down-regulating proto-oncogene 1 (ETS1). This study reveals that miRNA-451a-ETS1 axis dysfunction is a novel molecular mechanism that underlies the pathogenesis of childhood asthma [40]. A study has shown that miR-1165-3p targets IL-13 and PPM1A to control Th2 differentiation and pulmonary inflammation in asthma. miR-1165-3p inhibits the Th2 response of allergy through the STAT and AKT signaling pathways by targeted inhibition of protein phosphatase, Mg 2+/Mn 2+ – dependent 1A (PPM1A), thus proving that miR-1165-3p and PPM1A may be effective targets for the prevention and treatment of allergic asthma and related diseases [41]. The miR-29c/B7-H3 axis plays an important role in asthmatic children by regulating Th2/Th17 cell differentiation, and may provide a new target for asthma treatment [42]. The role of Th2-mediated microRNAs in asthma are summarized in the **Table 1** (**Figure 1**).

Altered MiRNA	Expressi-on pattern	Targets/ Regulators	Signaling Pathway	Function	Ref
miR-24 miR-27	Down-regulated	IL-4		limit IL-4 production	[15]
miR-145	Up-regulated	IL-5, IL-13		promote the production of Th2 cytokines	[14]
miR-1248	Up-regulated	IL-5		elevates Th2 cytokine levels.	[17]
miR-106a	Up-regulated	IL-10		regulate Th2 cytokine secretion	[19]
miR-17 ~ 92 cluster /miR-19a	Up-regulated	IL-13	NF-κB, JAK–STAT/ PI (3)K pathways	promotes Th2 cytokine production	[20]
miR-146a	Up-regulated	IL-5, IL-13		reduce the levels of IgE and T-helper 2 cytokines	[21]
miR-155	Up-regulated	IL-4, IL-5 IL-13		regulate Th2 cell differentiation and the secretion of IL-4, IL-5 and IL-13	[22, 23]
Let-7a	Down-regulated	IL-13		targeting IL-13 alleviates asthmatic phenotype	[24]
miR-410	Down-regulated	IL-4 IL-13		reduce the expression of IL-4 and IL-13	[25]
miR-135a	Down-regulated	TNF-α, IL-6, IL-5		Reduce airway inflammation	[26]
miR-34/449	Down-regulated	IL-13		Regulate differentiation of epithelial cells	[30]
miR-221-3p	Down-regulated	IL-4, IL-5, IL-13		correlate the type 2 status in asthma.	[31]
miR-26a, miR-146a, miR-31	Up-regulated	IL-5, IL-8, IL-12, TNF-α		Promote the expression of cytokines	[32]
mir27b, mir206, mir106b, mir203, mir23b				Reduce the production of cytokines in Th2 cells	[33]
miR-371, miR138, miR-544, miR-145 miR-214	Up-regulated	Runx3	—	regulates Th1/Th2 balance in asthma.	[34]
miR-21	Up-regulated	IL-12p35	IL-13Rα1, STAT6	regulates Th1 to Th2 phenotypic transformation	[16]
miR-29b	Down-regulated	T-box IFN-γ		regulate Th1 / Th2 balance in asthma	[35, 36]

Altered MiRNA	Expressi-on pattern	Targets/ Regulators	Signaling Pathway	Function	Ref
miR-92b, miR-210, miR-34a	Down-regulated			regulate Th2 polarization and dendritic cell maturation.	[37]
miR-29c	Up-regulated		miR-29c / B7-H3	regulate Th2/Th17 cell differentiation an	[42]
miR-126	Down-regulated			inhibit Th2-driven airway inflammation	[39]
miRNA-451a	Down-regulated	ETS1	miRNA-451a-ETS1	inhibit Th2 cell differentiation	[40]
miR-1165-3p	Down-regulated	IL-13 and PPM1A		Suppresses Th2 differentiation	[41]
miR-21 miR-19a				promoting differentiation of T cells towards Th2	[16, 43, 44]

Table 1.
Regulation of Th2 in asthma by miRNAs.

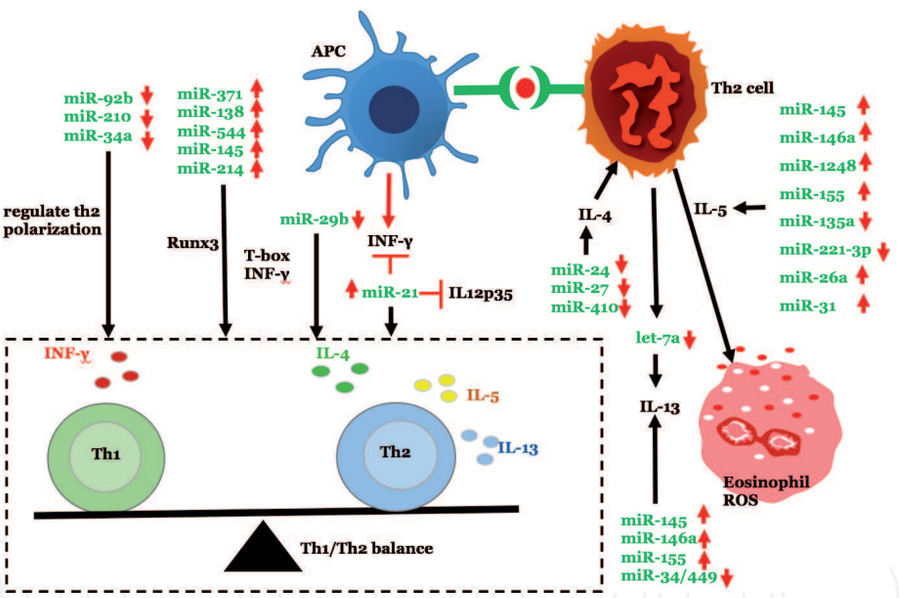


Figure 1.
Regulation of Th2 in asthma by miRNAs. Th1 and Th2 are in equilibrium. miR-34a, miR-92b and miR-210 regulate Th2 polarization. MiRNAs such as miR-371, miR-138, miR-544 and miR-145 affect Th1/Th2 balance of asthma by regulating Runx3. MiR-21 regulates Th1 and Th2 balance by regulating IL-12p35 transcripts. As shown in the figure, miR-24, miR-27, miR-410, let-7a, miR-145, miR-146a, miR-1248 and other miRNAs regulate the secretion of Th2 cytokines, such as IL-4, IL-5 and IL-13, through up-regulation or down-regulation in asthma, and affect the occurrence and development of asthma.

3. lncRNA regulate Th2 response in asthma

LncRNA refers to a class of RNA molecules with a length greater than 200 nucleotides which do not have the function of coding RNAs. LncRNAs are mainly involved in gene expression regulation at the transcription, post-transcription, translation and epigenetic levels, and are widely involved in various life processes such as cell proliferation, differentiation, apoptosis, migration, aging and metabolism [45, 46]. Abundant expressions of lncRNAs were found in T cell lineages,

suggesting that these transcripts play important roles in T cell development and differentiation [47]. Studies have found that some lncRNAs play important roles in the pathogenesis of asthma by regulating Th1/Th2 balance and Th2 inflammatory response [3, 48]. Understanding how lncRNAs alter gene expression to promote Th2 skewing may provide new insights into mechanisms and therapeutic targets for asthma.

3.1 Regulation of Th1/Th2 balance by lncRNAs

The gene encoding lncRNA MALTA1, a highly conserved nuclear lncRNA, is located on chromosome 11 (11q13.1). MALTA1 is highly expressed in most cells [49]. Liang et al. [50] conducted a cohort study of 772 asthmatic patients and 441 healthy controls, and found that the expression of MALAT1 was up-regulated and the expression of miR-155 was down-regulated in the blood of asthmatic patients. MALAT1 expression was inversely associated with impaired lung function and the Th1 / Th2 ratio, suggesting that its role was to impairs lung function by promoting the Th2 response. That is, the up-regulated expression of MALAT1 can induce the production of Th2 cytokines and inhibit the release of Th1 cytokines. Further study of the experiment showed that MALAT1 sponging miR-155 could alter the Th1/Th2 balance within CD^{4+} T cells through cytotoxic T-lymphocyte antigen 4 (CTLA-4) dependent mechanism. This study highlights the novel role of lncRNA MALTA1 in the development of Th2 in asthma. Wei et al. found that lncRNA PVT1 expression was increased in ozone-induced mouse asthma models, and the lncRNA PVT1-miR-15a-5p axis promoted Th1/Th2 imbalance in CD4 + T cells by activating the PI3K-Akt- signaling pathway [51].

3.2 lncRNA regulate Th2-type inflammation in asthma

Zhu et al. assessed expression of lncRNAs in peripheral blood samples of patients with eosinophilic asthma, neutrophilic asthma and healthy controls using RNA-sequencing. In this study, it was found that the expression of LNC_000127 was increased in eosinophilic asthma, and knockdown of LNC_000127 (refer to this article for details) reduced the expression of CCR8, CRLF2, and CD40L (Th2 inflammatory receptor). Targeting LNC_000127 may effectively reduce Th2 inflammation in eosinophilic asthma [52]. It has been demonstrated that induced pluripotent stem cells (iPSCs)-mesenchymal stem cells (MSCs) can effectively inhibit airway allergic inflammation in mice, and significantly reduce the expression levels of immunoglobulin (Ig) E and Th2 cytokines [53]. Further studies by Wang et al. [54] found that lncRNA MM9lincrnaexon12105 + and AK089315 were up-regulated in a model of ova-induced asthma. These two lncRNAs may be the main therapeutic targets of induced pluripotent stem cell mesenchymal stem cells (iPSC-MSCs) and may be involved in the regulation of Th2 type inflammation in asthma. This study provides an important basis for the study of the potential mechanisms of airway allergic inflammation and iPSC-MSC immune regulation, and these abnormal lncRNAs may become potential targets of allergic inflammation and iPSC-MSC mediated immune regulation. Wang et al. [55] conducted next-generation sequencing analysis of lncRNA and mRNAs on CD4 + T cells from ovalbumin-induced acute asthma mice and control mice, constructed co-expression networks of lncRNA and mRNAs, and found that lncRNA Fantom3_9230106C11 was decreased in Th2 cells. Further qRT-PCR verification showed that lncRNA Fantom3_9230106C11 could regulate the differentiation of Th2 cells. This study provides a platform to elucidate the role of lncRNA in Th2 differentiation and the pathogenesis of asthma. The role of Th2-mediated lncRNA in asthma are summarized in the **Table 2** (**Figure 2**).

Altered lncRNA	Expression pattern	Targets/ Regulators	Signaling Pathway	Function	Ref
MALTA1	Up-regulated		MALAT1 / miR-155 / CTLA-4	regulate Th1 / Th2 balance in asthma	[50]
lncRNA PVT1	Up-regulated	—	lncRNA PVT1-miR-15a-5p-PI3K/AKT/mTOR axis	regulate Th1 / Th2 balance in asthma	[51]
LNC_000127	Up-regulated	—	—	reduce Th2 inflammation	[52]
MM9lincrnaexon12105 + and AK089315	Up-regulated	—	—	regulate Th2-type inflammation in asthma.	[54]
lncRNA Fantom3_9230106C11	Down-regulated	—		Regulate the differentiation of Th2 cells.	[55]

Table 2.
lncRNA regulate Th2 response in asthma.

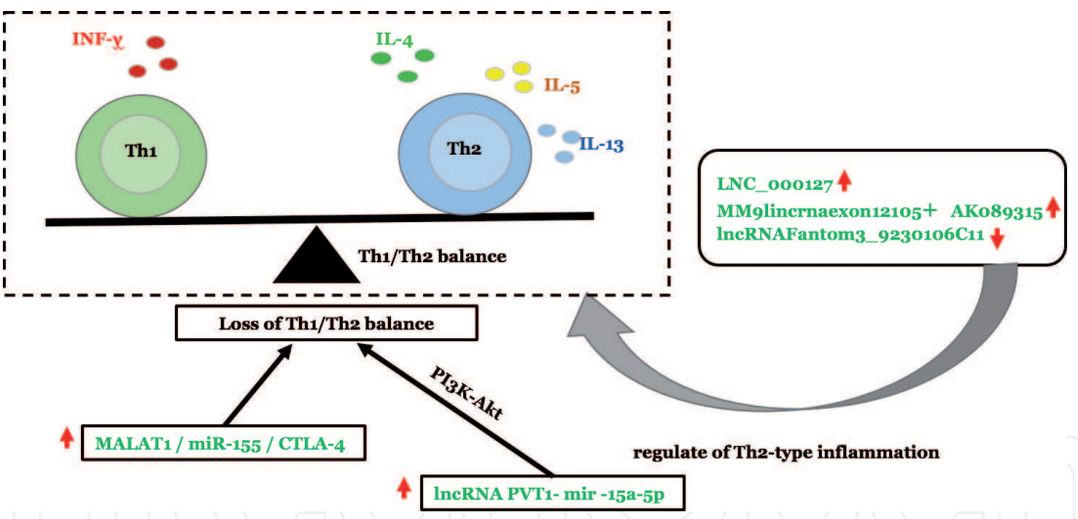


Figure 2.
lncRNA regulate Th2 response in asthma. MALAT1 sponging miR-155 could alter the Th1/Th2 balance within CD^{4+} T cells through CTLA-4 dependent mechanism. lncRNA PVT1-miR-15a-5p axis promoted Th1/Th2 imbalance in CD4 + T cells by activating the PI3K-Akt- signaling pathway. LNC_000127, MM9lincrnaexon12105 + and AK089315 and lncRNA Fantom3_9230106C11 primarily regulate the Th2-type inflammation.

4. circRNAs regulate Th2 response in asthma

CircRNAs compose a novel class of ncRNAs characterized by covalently closed-loop structures [56]. CircRNAs typically act as molecular sponges to bind and inhibit the transcription or activity of microRNAs (miRNAs), thereby affecting downstream mRNA expression [57]. CircRNAs are involved in the pathogenesis of

various diseases [58]. The role of circRNA in asthma regulation is still in its infancy, and there are relatively few studies on the role of circRNA in the pathogenesis of asthma, especially Th2 inflammation in asthma.

Huang et al. [59] confirmed the expression of hsa_circ_0002594 in CD4 + T cells in asthmatic patients and healthy subjects by quantitative real-time PCR (qRT-PCR) using circRNA microarray analysis (such as a student's *t* test, nonparametric tests, Spearman's rank-order correlation, Fisher's exact test, and the generation of receiver operating characteristic curves). Their data suggest that hsa_circ_0002594 is upregulated in CD4 + T cells of asthmatic patients, which may have potential value in the diagnosis and treatment of Th2-mediated allergic asthma. In a mouse model of HDM-induced asthma, the results revealed that the relative expression levels of circ_0000629 and circ_0000455 in the asthma group were significantly increased compared with those animals in the control group, whereas the expression levels of circ_0000454 and circ_0000723 were significantly decreased [60]. The circRNA-miRNA regulatory network indicated that two of the downregulated circRNAs (circ_0001454 and circ_0000723) targeted miR-146b and miR-214, and two of these upregulated circRNAs (circ_0000455 and circ_0000629) could target miR-29b and miR-15a [60]. The expression levels of inducible co-stimulator, a target gene of miR-29b, were also previously shown to be elevated in the lungs of asthmatic mice, and promoted Th2 cytokine production and eosinophilic inflammation [61]. Furthermore, vascular endothelial growth factor, which is a target gene of mir-15a, was shown to be overexpressed in cases of Th2-mediated lung inflammation, such as asthma, and induced an asthma-like phenotype [62]. By contrast, two of the downregulated circRNAs (circ_0001454 and circ_0000723) targeted miR-146b and miR-214, respectively, which were previously shown to be positively associated with asthma [34, 63]. Huang et al. found that hsa_circ_0005519 may induce IL-13 and IL-6 expression by regulating hsa-let-7a-5p in $CD4^+$ T cells to affect asthma. And hsa_circ_0005519 may be a potential biomarker of asthma [64]. The role of Th2-mediated circRNAs in asthma are summarized in the **Table 3** (**Figure 3**).

Altered circRNA	Expressi-on pattern	Targets/ Regul-ators	Signaling Pathway	Function	Ref
hsa_circ_0002594	Up-regulated	—	—	diagnosis and treatment of Th2-mediated allergic asthma	[59]
circ_0000629	Up-regulated	miR-29b, miR-15a	—	Regulate Th2 cytokine production	[34, 60–63]
circ_0000455	Up-regulated				
circ_0001454	Down-regulated	miR-146b, miR-214	—		
circ_0000723	Down-regulated				
hsa_circ_0005519	Up-regulated	Hsa-let-7a-5p	—	relieve suppression for IL-13/IL-6 in $CD4^+$ T cells.	[64]

Table 3.
circRNAs regulate Th2 response in asthma.

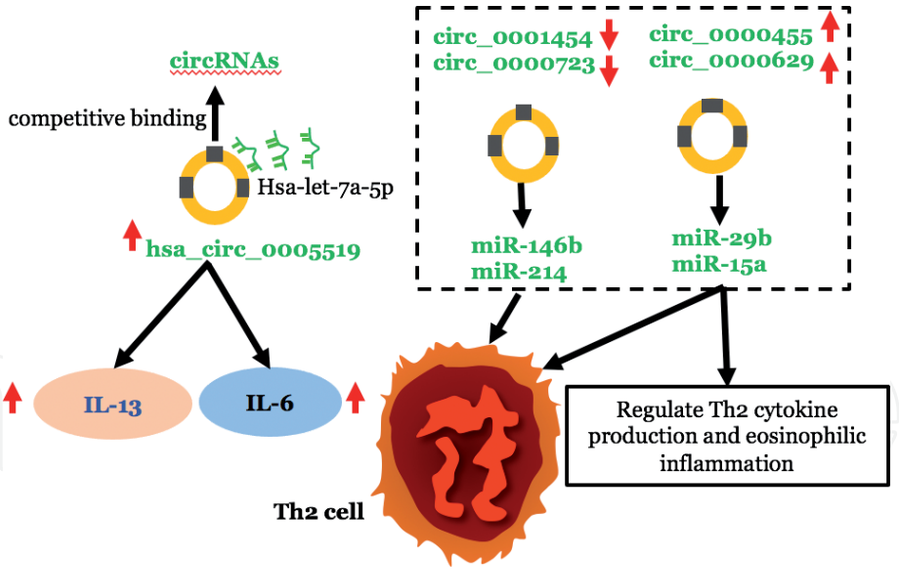


Figure 3.
circRNAs regulate Th2 response in asthma. Hsa_circ_0005519 functions as an endogenous hsa-let-7a-5p sponge to regulate the hsa-let-7a-5p/IL-13/IL-6 pathway in $CD4^+$ T cells. Two down-regulated circRNAs (circ_0001454 and circ_0000723) targeted miR-146b and miR-214, while two up-regulated circRNAs (circ_0000455 and circ_0000629) targeted miR-29b and miR-15a. These four circRNAs regulate TH2 cytokine production by targeting miRNA.

5. Summary

NcRNAs display a wide range of functions, and each ncRNA has its own characteristics. This chapter mainly summarized the regulation of Th2 differentiation and immune response in asthma and experimental models of disease.

The role of miRNA in regulating Th2 cell-mediated inflammation in asthma is mainly reflected in several aspects: regulating Th1/Th2 balance, influencing cytokine secretion and regulating the activation state of T cells. The pathway of regulation can be that a single miRNA regulates one or more mRNAs, or multiple miRNAs of one or more gene clusters synergistically act on one or more mRNAs to exert biological effects. LncRNA plays a similar role to miRNA in regulating Th2 cell-mediated inflammation in asthma, affecting its activation, transformation and cytokine secretion. Most of the existing studies only analyzed the expression profile of lncRNA and identified the differentially expressed lncRNA molecules, but did not conduct in-depth study on its precise molecular mechanism. CircRNAs may play important roles in Th2 cells differentiation and, thus, play regulatory roles in Th2 cell-mediated inflammation in asthma. They can act as competitive endogenous RNAs (ceRNAs, which can regulate each other by competitively binding common microRNA response elements) of miRNAs to exert their biological effects, but the specific mechanism needs to be further studied.

In conclusion, miRNA, lncRNA and circRNA play important roles in regulation of Th2 cell function in asthma. However, the exact molecular mechanism of ncRNA in the regulation of TH2 cell function in asthma remains to be determined. Therefore, how to find out functional ncRNAs and elucidate their precise functions present the difficulties and challenges in the study of ncRNAs in this field. In future, more and more ncRNAs involved in the pathogenesis of asthma will be discovered, and the role of ncRNAs in the inflammatory process mediated by Th2 cells will be revealed. This will provide new details in the pathogenesis of asthma, and will help to develop new biomarkers and molecular targets for the diagnosis, classification, and treatment of asthma.

Conflict of interest

The authors declare no conflict of interest.

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