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REVIEW ARTICLE

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Involvement of microRNAs in physiological and pathological processes in asthma

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Abstract

Asthma is the most common respiratory disease accompanied by lung inflammatory disorders. The main symptoms are airway obstruction, chronic inflammation due to mast cell and eosinophil activity, and the disturbance of immune responses mostly mediated by the Th2 response. Genetic background and environmental factors also contribute to the pathogenesis of asthma. Today, microRNAs (miRNAs) are known as remarkable regulators of gene expression. As a small group of noncoding single-strand RNAs, mature miRNAs (~21 nucleotides) modulate the gene expression by targeting complement RNAs at both transcriptional and posttranscriptional levels. The role of miRNAs in the pathogenesis of many diseases such as allergies, asthma, and autoimmunity has been vastly studied. This review provides a thorough research update on the role of miRNAs in the pathogenesis of asthma and their probable role as diagnostic and/or therapeutic biomarkers.

KEYWORDS

asthma, diagnostic and therapeutic biomarkers, microRNAs

1 | INTRODUCTION

According to the Global Initiative for Asthma (GINA), *"asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation"* (Reddel, Levy, Global Initiative for Asthma Scientific, Dissemination, & Implementation, 2015). Exposure to pollen, dust mites, and allergens can exacerbate asthma attacks (Jayasinghe, Kopsaftis, & Carson, 2015; Neder, Nery, Silva, Cabral, & Fernandes, 1999). Although the exact underlying mechanism of asthma is not yet understood, it is believed that a combination of the genetic, epigenetic, and environmental factors are involved. Moreover, increased use of antibiotics, obesity, airways inflammation, and genetic background are among the major risk factors of asthma.

In the last half-century, a significant increase occurred in allergic diseases due to the expansion of urbanization and industrialization, whereas fewer cases were reported from rural areas (Kudo, Ishigatsubo, & Aoki, 2013). Today, 300 million people worldwide are suffered from asthma (most of which are children) with annually 250,000 mortality rate, and it is anticipated that another 100 million people will be added by 2025 (Corren et al., 2011). Proper and effective treatment can significantly improve physical performance, quality of life, and mortality rate of asthma (Bahadori et al., 2009). Now, more than $6.2 billion is estimated to be spent annually for the management of the disease. Asthma treatment involves the use of short- and long-acting beta agonists, leukotriene antagonists, allergen immunotherapy, and corticosteroids. Although inhaled corticosteroids have been introduced as the main line of asthma treatment in the past two decades with remarkable therapeutic outcomes, there are some side-effects and also resistant to treatment in patients (Corren et al., 2011). The immune responses especially Th2 cell responses play a critical role in asthma pathogenesis and its exacerbations. Th2 cytokines including IL-4, IL-5, IL-9, and IL-13 increase airway sensitivity, mucosal secretion, eosinophilic permeability, and IgE secretion in the bloodstream (Kudo et al., 2013). The IgE secretion results in the production and release of metabolites including histamine and leukotriene, which cause the contraction of smooth muscles and airway edema (Platts-Mills, 2001; Wenzel, 2012).

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Among various genetic and epigenetic factors, microRNAs (miRNAs) play important roles in the pathogenesis of asthma and allergic diseases, as critical regulators of gene expression. Several recent studies evaluating the role of miRNAs in the pathogenesis and exacerbation of asthma have concluded, if recognized completely, miRNAs could be used as applicable diagnostic/therapeutic biomarkers for asthma management. In this review, the role of miRNAs in the pathogenesis of asthma and the extent to which they are expressed in different samples, such as lung tissue, blood, bronchoalveolar lavage fluid (BALF), and sputum in asthmatic patients is discussed. Furthermore, their role as diagnostic and therapeutic markers in various stages of the disease are investigated.

2 | MicroRNAs: BIOGENESIS, FUNCTION, AND ROLE

In 1993, R. C. Lee, Feinbaum, and Ambros (1993) discovered the first miRNA (*Lin*-4) in *Caenorhabditis elegans*. They found that *Lin*-4 plays important roles in gene expression regulation. Then, Reinhart et al. (2000) discovered the second miRNA, *Let*-7 in 2000. Since then, many studies have investigated the nature and also the role of miRNAs in the pathogenesis of several diseases (Griffiths-Jones, Saini, van Dongen, & Enright, 2007; Table 1). miRNAs are a small group of noncoding single-stranded RNAs containing ~21 nucleotides that mostly are transcribed by RNA polymerase II. They bind generally to the 3′-untranslated region (3′-UTR) of their target mRNAs and induce posttranscriptional or translational silencing processes (Nilsen, 2007). Due to their specific small structure, miRNAs have unique features. The processing and biogenesis of miRNAs are performed within two separate locations, including the nucleus and cytoplasm. Within the nucleus, RNA polymerase II transcribes miRNA genes into pri-miRNA with a hairpin structure containing a poly A region at 3′ end and a cap at 5′ end. This structure is detected by the Drosha/DGCR8 complex in the nucleus and is cleaved into pre-miRNA. Pre-miRNA is transferred into the cytoplasm through Exportin5 and Ran-GTP. Dicer, an RNA endonuclease enzyme located in the cytoplasm is the final miRNA processor. Dicer, along with a two-stranded RNA-binding protein known as TRBP (Dicer/TRBP complex), cuts the ending loop of pre-miRNA making a two-stranded miRNA containing a guide and a passenger strand. The passenger strand is further destroyed and the guide strand is loaded into the Argonaute protein (Borish et al.) to create the RNA-induced silencing complex (RISC; Bacharier et al., 2008). The RISC complex screens cytosolic

TABLE 1 MicroRNAs involvement in various diseases

miRNA	Disease or site	Function	Ref. (PubMed IDs)
miR-208	Heart	It is essential to express the genes involved in the fibrosis of the heart and the growth of hypertrophy	17525252 & 16380711
miR-1	Heart	The primary function is cardiac growth, but by suppressing effective channels in the membrane resting potentials (such as KCNJ2 and GJA1), it can cause cardiac disorder and arrhythmias	17525252 & 16380711
miR-203	Skin	As the expression increases, it results in the suppression of SOCS-3, which is involved in inflammatory responses and keratinocyte function	17622355
miR-155	Rheumatoid arthritis	The expression of miR-155 in these patients suppresses the matrix metalloprotease-3 (MMP-3) and, by anti-inflammatory cytokines, it neutralizes the induction of Matrix metalloproteinase MMP-1 and MMP-3	18438844 & 18383392
miR-221/222	Thyroid papillary carcinoma	It affects p27Kip1, which is a tumor suppressor, reduces its expression, and can affect cell cycle, and cause the phase change from G1 to S	23023232 & 17914108
miR-221/21	Gastric cancer	Increasing its expression decreases the expression of RECK and cyclin-dependent kinase inhibitor 1B (CDKN1B) factors, and in the case of silencing of the miRNA, a significant decrease occurred in cell proliferation and migration, and the apoptosis increases	(Effatpanah et al., 2015) & 22994734
miR-34a	Prostate cancer	By targeting p53, it acts as a tumor suppressor and prevents metastasis and cancer spread	21240262
miR-31	Breast cancer	It can suppress metastatic cancer cells by targeting a group of prometastatic genes, including *RhoA* and *WAVE3*	22289355
miR-122	Liver	It has the highest frequency in the adult liver and is involved in homeostasis, cholesterol biosynthesis, and metabolism of fatty acids. Treatment with miR-122 supplements suppresses hepatitis C	19965718
miR-375	Diabetes	It is essential for the homeostasis of glucose and α- and β-cell turnover. Its absence results in an increase in the number of pancreatic alpha cells and glucagon levels, as well as in the reduction of beta cells and, subsequently, hyperglycemia. It is therefore considered as a possible predictor of diabetes	19289822
miR-29a/b-1	Alzheimer's disease	The enzyme beta-secretase 1 (BACE-1) plays an important role in Alzheimer's disease, and the decrease in miR-29a/b-1 is associated with an increase in the BACE-1 enzyme	18434550

mRNAs to identify the complement target RNAs. If the miRNA or mRNA sequence of the target is fully complemented, it would be destroyed (transcriptional silencing), and if mismatches were found, the translation would be suppressed. At last, both mechanisms make the target genes silent (Bartel, 2004; Krol, Loedige, & Filipowicz, 2010; I. Lee et al., 2009).

Besides intercellular signaling, some miRNAs play roles in intracellular signaling and cell–cell communication. Interestingly, body fluids such as blood, urine, milk, sweat, sputum, and tears contains special miRNAs known as circulating miRNAs. These miRNAs secreted from normal or damaged cells (J. W. Wang et al., 2011) are stable against the enzymatic digestion. Mostly, circulating miRNAs are packed in secreted particles to protect from ribonucleases. These miRNAs are more resistant to harsh environmental conditions such as repeated freezing and thawing, high salt concentrations, and also pH variations (Ruan, Fang, & Ouyang, 2009). Circulating microRNAs are poorly studied in asthmatic patients but have great potentials for diagnostic and therapeutic applications.

3 | INVOLVEMENT OF Th2 CELLS IN ASTHMA

Th2 cells induce humoral immune responses and are especially involved in allergic responses (Umetsu, McIntire, Akbari, Macaubas, & DeKruyff, 2002). By introducing allergens into the body, plasma cells begin to secrete IgE, which binds to the surface of mast cells and basophiles. Following re-introducing the same allergens and binding to the membrane-bound IgE, mast cells, and basophiles are stimulated and secrete various mediators such as histamine, and interleukins and cytokines such as IFN-γ and TNF (Balkissoon, 2008; Ngoc, Gold, Tzianabos, Weiss, & Celedon, 2005). Important cytokines and their role in the immunopathogenesis of asthma are summarized in Table 2.

4 | DIFFERENTIATION OF Th2 CELLS IN ASTHMA

Differentiating primary T cells into Th1 or Th2 requires the activation/suppression of some signaling processes in response to special cytokines as well as the strength of T cells receptor stimulator (TCR) activation. The strong activation of TCR tends to differentiate toward Th1 cells, but TCR weak signals favor the differentiation towards Th2 (Welte et al., 1999). Protein kinase C (PKC) is another factor mediating the differentiation and polarization of T cells. The stimulation of calcium signaling or inhibition of PKC promotes T cells differentiation towards Th1, whereas calcineurin inhibition or PKC stimulation tends toward Th2 (Noble et al., 2000). The nuclear factor of activated T cells (NFAT) is also another signaling pathway for T cells polarization. Calcium plays a significant role in regulating three important proteins in this

TABLE 2 Important cytokines in the immunopathogenesis of asthma.

T cells	Cytokine	Function	Ref. (PubMed IDs)
Th1	IFN-γ	Switching immunoglobulins to produce IgG Increasing phagocytosis by macrophages Enlargement or facilitating the practice of trapping microbes	21377040, 16906156, 11397944, 21737883
	TNF	Activation of neutrophils Promoting inflammation	17475560, 11405550, 11264706
	IL-12	Inhibiting IgE production Antimicrobial, antiparasitic, and antitumor activities of macrophages	18206717, 9860244, 17056578
Th2	IL-4	Prevention of apoptosis by T cells Ability to recruit and increase the adhesion of immune cells to inflammation sites Increasing mucosal secretion by inducing mucin gene expression Airway obstruction	10588591, 10229869, 12042806, 12145657
	IL-5	Affecting the survival, differentiation, and migration of eosinophils Eosinophilic inflammation by increasing the expression of IL-5Rα in $CD34^+$ cells	10229869, 11292022, 12649124, 9366561, 11529906
	IL-6	Increasing Th2 Increased eosinophilia Impacting mast cells Increased airway responsiveness	16129910, 23136556
	IL-13	Increased eosinophilic secretion Inflammation of the airway by increasing the expression of CCL-11 chemokine Increased mucus secretion from STAT6 Maintaining IgE production Synergistic effects with TNF-α or IL-5 for the activation of eosinophils	12091879

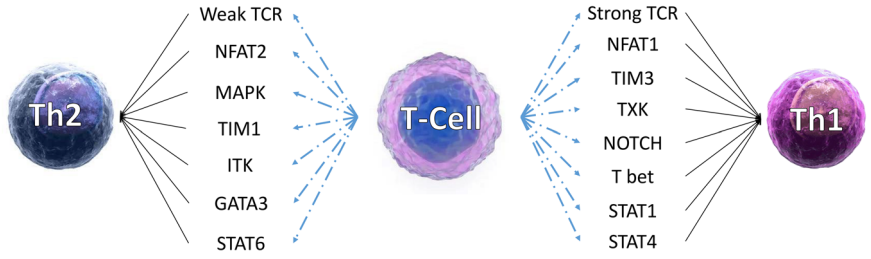

FIGURE 1 Effective factors for differentiation of T cells into Th1 and Th2 cells [Color figure can be viewed at wileyonlinelibrary.com]

pathway. NFATs can effectively induce several interleukins or indirectly interact with some transcription factors to differentiate T cells (Scheinman & Avni, 2009). NFAT proteins can also affect the strength of TCRs to differentiate T cells. A poor TCR signal stimulates some NFATs that induce the expression of IL-4 and result in Th2 cells. On the other hand, a strong TCR signal can result in the increase of positive interferon regulators and subsequently lead to Th1 (Z.-Y. Wang et al., 2006).

Tec kinase and mitogen-activated protein kinase (MAPK) are other important factors for the polarization of T cells. Tec kinase is activated by Src kinases after TCR ligation. Following a weak TCR signal, a member of this family known as IL-2-inducible T cell kinase (ITK) induces the differentiation of Th2 by inhibiting the expression of T-bets. However, TXK (Rlk in mice), another member of this family, is a specific transcription factor for Th1 cells that transcribes IFN-γ. The detailed mechanism of ITK and TXK for differentiating Th1/Th2 shift is not still completely understood (Andreotti, Schwartzberg, Joseph, & Berg, 2010; Readinger, Mueller, Venegas, Horai, & Schwartzberg, 2009). In contrast, MAPK is activated after the TCR stimulation. The key factors of this pathway include extracellular signal-regulated kinase (Brunekreef et al., 2002), c-Jun N-terminal kinase (JNK), and p38 (Chow, Dong, Flavell, & Davis, 2000). These proteins regulate the expression of interleukins (such as IFN-γ and IL-4) and transcription factors (such as STAT6 and GATA3) and are effective to shift towards Th2 (Dodeller, Skapenko, Kalden, Lipsky, & Schulze-Koops, 2005; So, Oh, Jang, Kim, & Lee, 2007). In addition, T cell immunoglobulin and the mucin-domain-containing (TIM) are a family of cell surface receptors that regulate T cell activation and apoptosis and are involved in Th1/Th2 immune responses. TIM3 is expressed specifically in Th1 cells, whereas TIM1 is expressed preferentially in Th2 cells. It has been shown that Th1 and Th2 cells act differently in apoptosis-sensitive conditions, where Th2 cells are more resistant to apoptosis than Th1 (Nakae et al., 2007).

Notch signaling is also among the important regulators of cell differentiation whose role is still not completely appreciated. The induction of Notch promotes the T-bet expression and thus induces Th1 differentiation. Notch can also induce Th1 specific genes through the interaction with NF-κB, P50, and P65 (Radtke, Fasnacht, & MacDonald, 2010).

T-bet, also known as Tbx21, is considered as the main regulator of Th1 cells. The IFN-γ/STAT1 signaling also plays an important role in controlling the specific expression of Th1 cells (Szabo et al., 2000). The IL-12/STAT4 pathway affecting T-bet has also been discussed in the literatures. It has been reported that by inducing the IL-12Rβ2 expression, the signaling function of IL-12/STAT4 of Th1 cells is affected. Furthermore, T-bet associates and interacts with Runt-related transcription factor 3 (RUNX3) and H2.0-like homeobox protein (HLX; two other transcription factors) to regulate the differentiation of Th1 cells and production of IFN- γ. It has been proposed that by controlling the expression of GATA3, T-bet can inhibit the development of Th2 cells (Usui, Nishikomori, Kitani, & Strober, 2003). On the other hand, STAT6 signaling axis is active in Th2 cells. Besides IL-4, other stimuli such as B cell receptor (BCR), TCR, CD40, and CD28 can also activate STAT6 and lead to Th2 differentiation and Th1 shift inhibition. Serine phosphorylation regulates the STAT6 transcription. In addition, IFN-α, IL-3, IL-15, and platelet-derived growth factor (PDGF) can cause the phosphorylation of STAT6. IL-4 phosphorylates serine 756 and induces STAT6 (Wei et al., 2010). Thus, T-bet, STAT1, and STAT4 signaling along with the effects of IFN-γ and IL-12 proteins activates Th1 cells and lead to the production of different cytokines. On the other hand, following the action of IL-4, GATA3, and STAT6 pathways would lead to the polarization and activation of Th2 (Figure 1; Mjösberg et al., 2012; Nakayamada et al., 2014).

5 | MicroRNAs: THEIR FUNCTIONS IN ASTHMA

Despite significant advances, multifactorial nature and ambiguous pathophysiology have complicated the control and prevention of asthma, and due to the lack of diagnostic biomarkers, the definitive diagnosis of the disease is still challenging (Macdonald, Sternberg, & Hunter, 2007). Interestingly, recent progressions in the identification and characterization of several miRNAs have opened new insights into asthma management (Ariel & Upadhyay, 2012). Some miRNAs proposed to be used in the control and prevention of asthma are more described here.

5.1 | miR-145

A study showed that the expression induction of miR-146a could inhibit bronchial cell proliferation by affecting epidermal growth factor receptor (EGFR) and possibly increasing apoptosis. This miRNA seems to activate the P-ERK signaling pathway, increase the activity of

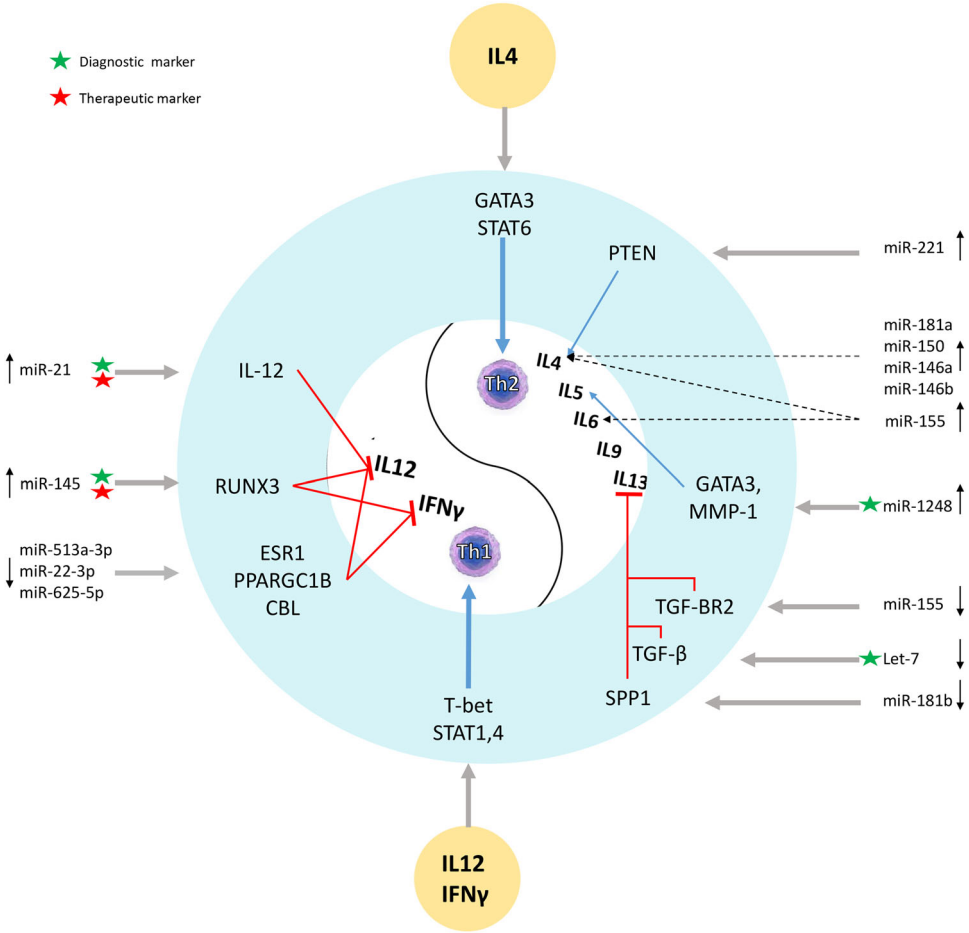

FIGURE 2 miRNAs therapeutic and diagnostic applications. Upregulation or downregulation of miRNAs with clinical potentials (indicated with asterisk) inhibit or activate the expression of target genes in Th1/Th2 arms of immune system, directly or indirectly [Color figure can be viewed at wileyonlinelibrary.com]

caspase-3/7, and decrease the expression of *Bcl-2* (Y. Zhang et al., 2016). Another miRNA that can be used as a marker for asthma diagnostic and therapeutic purposes is miR-145. The overexpression of this miRNA leads to the inhibition of Runx3 and affects the Th1/Th2 balance. Runx3 is a member of the runt domain family of transcription factors expressing in peripheral blood, tissue, and immune cells with a potential relationship with gastric and epithelial originated cancers. Runx3 can shift cellular differentiation towards Th1 cells with positive feedback on the T-bet pathway and weakening the GATA3 pathway. As a result, due to significant effects on Runx3, miR-145 can be a diagnostic and therapeutic marker (Fan et al., 2016).

5.2 | miR-21

miR-21 is a critical miRNA that functions in many diseases, including cardiovascular diseases, cancer, and asthma. The miR-21 can be a potential diagnostic/therapeutic molecule for regulating the polarization and proliferation of T cells. The miR-21 targets IL-12 that, in turn, induces IFN-γ production, differentiates to Th1 cells, and inhibits significantly the production of IgE. In addition, miR-21 is stimulated via IL-13 and targets the *IL-12* gene that leads to Th2 polarization (Elbehidy et al., 2016). Another study evaluating miR-21 found that the increased expression of miR-21could result in the pathogenesis of asthma by two ways: Inhibiting the *IL-12* gene, and through GATA3 that directly induces the differentiation of Th2 cells. This study along with another review article introduced miR-21 as a potential diagnostic/therapeutic marker (V Sawant et al., 2015; Wu et al., 2014).

5.3 | miR-138

According to the reports, miR-138 is reduced in asthmatic individuals. This miRNA can suppress tumor growth through the inhibition of enhancer of Zeste Homolog2 (EZH2), bind to PDK, and directly suppress the PI3K/AKT pathway (as an important and vital pathway for the differentiation, growth, and expression of proteins). As a result, the expression of miR-138 results in the inhibition of cell proliferation, and therefore, it could be a therapeutic marker for the PI3K/AKT pathway (Y. Liu, Yang, Sun et al., 2015). TGFB1 is a key mediator in the pathogenesis of asthma and can increase the cell proliferation and induction of fibronectin proteins, collagen, and elastin in the extracellular matrix (ECM).

TABLE 3 Therapeutic and diagnostic microRNAs

Process	Therapeutic/ diagnostic	miRNA	Target Gene	Alternation	Sample	Study population	Ref. (PubMed IDs)
Cell cycle	Therapeutic and diagnostic	miR-146a	*EGFR*	Up	Plasma	Patients with asthma (30) versus healthy control (30)	27446287
Cell cycle	Therapeutic	miR-138	*PDK1, PTEN*	Down	Lung (airway smooth muscle cells)	Patients with asthma versus healthy control	26151666
Cell cycle	Therapeutic	miR-143-3p	*TGFB1, NFATc1*	Down	Lung (airway smooth muscle cells)	Patients with asthma (9) versus healthy control(9)	27639060
Cell cycle	Therapeutic	miR-20b	*VEGF*	Down	Alveolar macrophages	Patients with asthma versus healthy control	22324377
Th1	Therapeutic and diagnostic	miR-145	*RUNX3*	Up	Peripheral blood	Patients with asthma (59) versus healthy control (49)	27902892
Th1	Therapeutic and diagnostic	miR-21	*IL-12 mRNA*	Up	Serum	Patients with asthma (95) versus healthy control (80)	26874829
Th1	Therapeutic and diagnostic	miR-21	*IL-12 mRNA*	Down	Serum	Patient with asthma and steroid sensitivity (40) versus patients with asthma (40)	26874829
Th1	Therapeutic and diagnostic	miR-21	*IL-12 mRNA*	Up	Serum	Patients with asthma and steroid resistance (15) versus patients with asthma and steroid sensitivity (40)	26874829
Th1	Therapeutic and diagnostic	miR-21	*IL-12 mRNA*	Up	Serum	Patients with asthma (8) versus healthy control (8)	25707810
Th1	Therapeutic and diagnostic	miR-21	*IL-12 mRNA*	Up	Lung (bronchial epithelial cells)	Treated patients with asthma (inhaled corticosteroids) (19), patients with asthma (nontreatment) (16) versus healthy control (12)	24995087
Th2	Therapeutic and diagnostic	miR-126	*IL-12 mRNA*	Up	Lung (bronchial epithelial cells)	Treated patients with asthma (inhaled corticosteroids) (19), patients with asthma (nontreatment) (16) versus healthy control (12)	24995087
Th2	Diagnostic	let-7a	*IL-13, ADRB2, TLR4, and TGF-ß receptor*	Down	Bronchial biopsy	Severe asthma (12), mild asthma (12) versus healthy control (10)	25130484
Th2	Diagnostic	miR-1248	*IL-5, IL-13, GATA3, FcεR1β, IL-1β, MMP-1, Mucin-1*	Up	Serum	Patients with asthma (10) versus healthy control (10)	23885321
Th2	Diagnostic	miR-26a	*TGF-β, CCR5, IL-4 Receptor, IL-6, Cox-2, TLR4, IFN-γ, ICOS*	Down	Serum	Patients with asthma (10) versus healthy control (10)	23885321
Th2	Diagnostic	Let-7a	*IL-13, TGF-β receptor, TLR4*	Down	Serum	Patients with asthma (10) versus healthy control (10)	23885321
Th2	Diagnostic	Let7d	*IL-13, TGF-β receptor, TLR4*	Down	Serum	Patients with asthma (10) versus healthy control (10)	23885321
Th2	Diagnostic	miRNA-1165-3p	NM	Up	Serum	Patients with asthma (53) versus healthy control (53)	30015513

TABLE 4 Expression of miRNAs in different samples in asthmatic patients

Sample		Expression	miRNAs
Blood	**Serum**	Up	miR-1248, miR-21
		Down	miR-26a, Let-7a, Let7d
	Plasma	Up	miR-126, miR-21, Let-7c, miR-1, miR-16, miR-299–5p, miR-146a, miR-150, miR-133b, miR-1248, miR-29, miR-422, miR-1291, miR-206, miR-328, miR-26a, miR-106a, miR-155
		Down	miR-181b-5p, miR-125b, Let-7b, Let-7e, miR-223, miR-570, miR-148a, miR-133a, miR-26b, miR-330-5p, miR-145, miR-144, miR-146a, miR-338-3p
	Peripheral blood	Up	miR-193, miRNA-221, miR-155, miR-145, miR-19a, miR-323-3p
		Down	miR-625-5p, miR-22-3p, miR-513a-5p, miR-192, miR-146a, miR-146a, miR-146b
Sputum		Up	miR-155, miR-629-3p, miR-223-3p, miR-142-3p
		Down	miR-155
Biopsy		Up	miR-19a, miR-21, miR-126, miR-145, miR-146, miR-221, miR-221, miR-498, miR-187, miR-498, miR-874, miR-143, miR-886-3p, miR-21, miR-487b, miR-181c, miR-let7f
		Down	miR-18a, miR-19b, miR-27b, miR-106b, miR-128, miR-155, MiR-181b-5p, MiR-181a-5p, let-7a, miR-221, miR-34c-5p, miR-449a, miR-449b-5p, miR-18a, miR-126, miR-155, miR-18a, miR-126, let-7E, miR-155, miR-224, miR-138, miR-143-3p, miR-203

5.4 | miR-143-3p

The interaction of nuclear factor of activated T-cells (NFATs) with TGFB1 is also evident in the pathogenesis of asthma. The decrease in the miR-143-3p level has been reported in asthma patients, and therefore, it has been reported that miR-143-3p can be used as a therapeutic marker for the suppression of NFAT and TGFB1 (Cheng et al., 2016).

5.5 | miR-20b

miR-20b is a miRNA targeting vascular endothelial growth factor (VEGF) as a proangiogenic factor. It has been recently recognized that alveolar macrophages are a major source of miR-20b, though epithelial and smooth muscles can express it. This miRNA is involved in the angiogenesis and increased vessel permeability (Song, Ma, Yao, Tao, & Gan, 2012).

5.6 | Let-7a

Let-7a is a potential diagnostic miRNA in asthmatic patients. This miRNA is the most abundant miRNA in lungs and plays an important role in pulmonary diseases such as asthma. Although Let-7a is usually decreased in asthma patients, its increase can suppress IL-13 and contribute to the regulation of Th2, and consequently, the pathogenesis of asthma. IL-13, Adrenoceptor beta 2 (ADRB2), toll-like receptor 4 (TLR4), and TGFB receptor are targets of Let-7a (Rijavec, Korošec, Žavbi, Kern, & Malovrh, 2014).

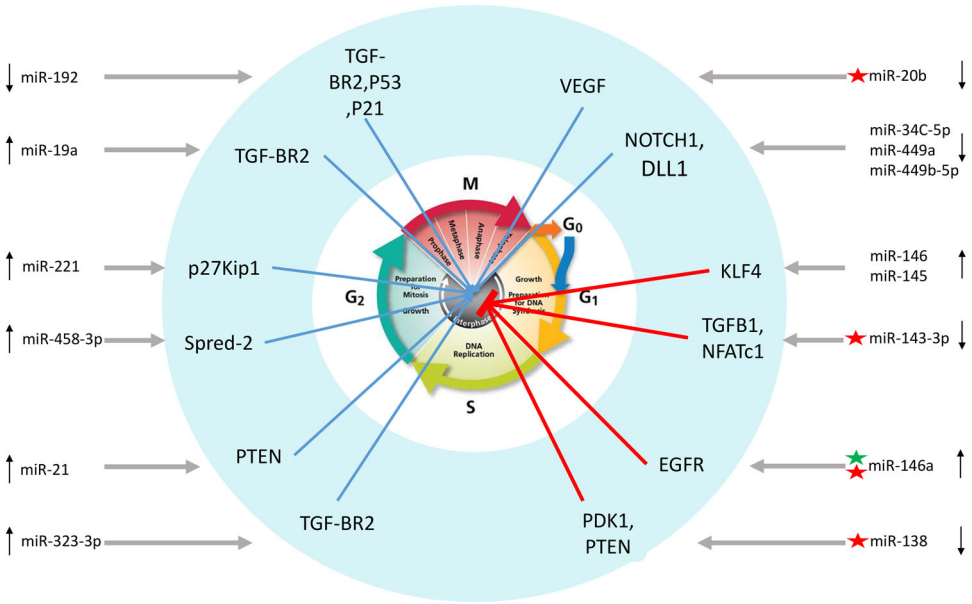

FIGURE 3 miRNAs and their targets in the cell cycle. Upregulation or downregulation of miRNAs can affect the expression of downstream target genes in cell cycle [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 5 miRNAs affecting cell cycle in asthma

miRNAs	Target gene	Alternation	Sample	Study population	Ref. (PubMed IDs)
miR-19a	*TGF-BR2*	Up	Lung (bronchial epithelial cells)	Severe asthma (6) versus healthy control (9)	25443138
miR-192	*TGF-BR2, P53, P21*	Down	Whole blood	Mild asthma (pre-challenge) (7) versus healthy control (4)	23170939
miR-221	*p27Kip1*	Up	Peripheral blood	Patients with asthma (8) versus healthy control (8)	22572970
miR-221	*Spred-2*	Up	BALF	Patients with asthma (6) versus healthy control (6)	22895815
miR-485–3p	*Spred-2*	Up	BALF	Patients with asthma (6) versus healthy control (6)	22572970
miR-21	*PTEN*	Up	Lung (airway smooth muscle cells)	Patients with asthma (3) versus healthy control (3)	26651881
miR-145	*KLF4*	Up	Airway smooth muscle (lung)	Asthma (treated with cytokines) (5) versus not treated (5)	26197891
miR-146	*KLF4*	Up	Airway smooth muscle (lung)	Asthma (treated with cytokines) (5) versus not treated (5)	26197891
miR-34c-5p	*NOTCH1, DLL1*	Down	Bronchial epithelial cells	Steroid-using subjects with asthma(19), steroid-naive subjects with asthma (16) versus healthy control (12)	22955319
miR-449a	*NOTCH1, DLL1*	Down	Bronchial epithelial cells	Steroid-using subjects with asthma (19), steroid-naive subjects with asthma (16) versus healthy control (12)	22955319
miR-449b-5p	*NOTCH1, DLL1*	Down	Bronchial epithelial cells	Steroid-using subjects with asthma (19), steroid-naive subjects with asthma (16) versus healthy control (12)	22955319
miR-323-3p	*TGF-b*	Up	Peripheral blood	Patients with asthma versus healthy control	27059796

Note: BALF: bronchoalveolar lavage fluid; miR: microRNA.

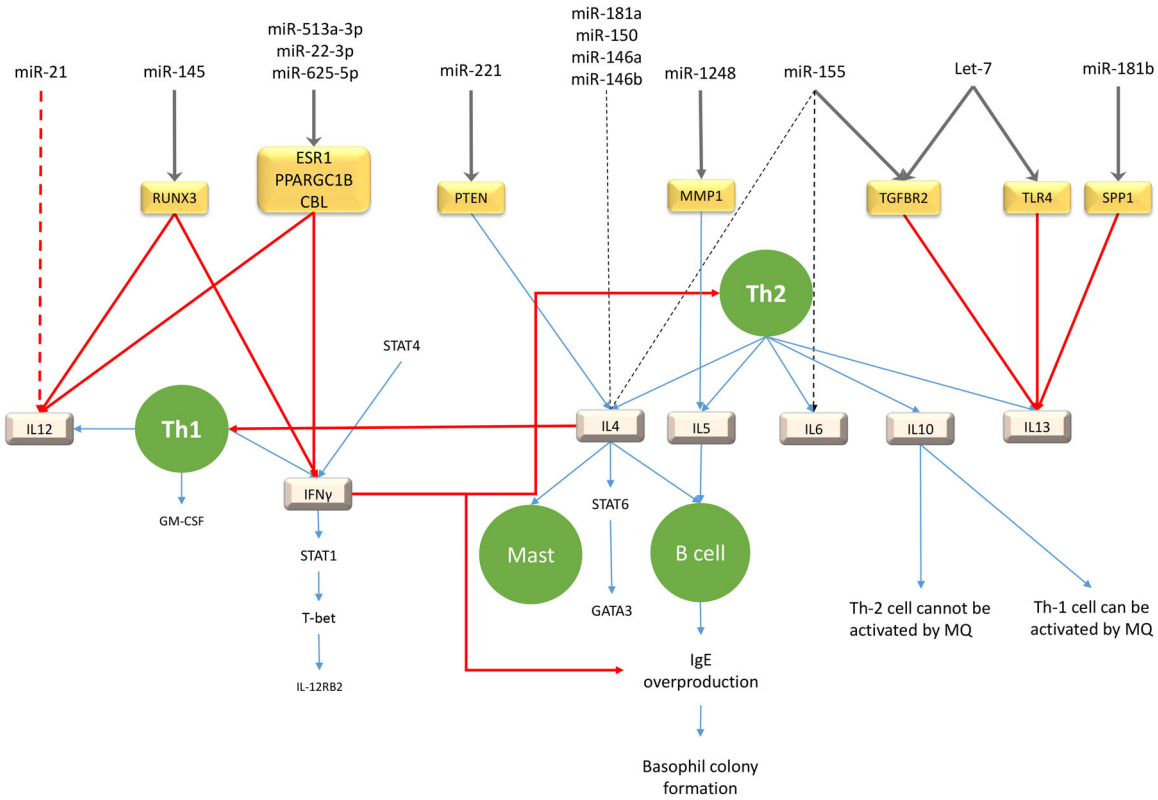

FIGURE 4 miRNAs targeting signaling molecules during Th1/Th2 differentiation. The expression of different cytokines in regulated by different miRNAs [Color figure can be viewed at wileyonlinelibrary.com]

5.7 | miR-1248

A review reported that among four miRNAs miR-1248, miR-26a, Let-7a, and Let7d, only miR-1248 was increased in asthma patients and the others were decreased. The miR-1248 targets IL-5, IL-13, and GATA3, and collaborates with IL-5 to contribute to the pathogenesis of asthma. So, miR-1248 can be suggested as a diagnostic asthma marker (Panganiban et al., 2012; Figure 2; Table 3).

Due to the importance of miRNAs in the diagnosis and treatment of asthma, many studies have evaluated different miRNAs in various clinical specimens of asthma patients, including lung biopsy and blood to candidate potential diagnostic/therapeutic biomarkers. Some of these studies and their results are listed in Table 4. As shown in Table 4, in most cases miRNA levels have been decreased.

6 | MicroRNAs: CELL PROLIFERATION IN ASTHMA

6.1 | miR17–92 family: miR-19a

miR-19a is a member of the miR17–92 family. It has been reported that in the absence of miR17–92 family, the mice urinary cortex does not evolve resulting in early death after the birth. miR-19a is increased during asthma and can enhance cell proliferation. Therefore, inhibiting miR-19a expression can augment the phosphorylation of SMAD3 by TGFB and subsequently suppress cell proliferation (Haj-Salem et al., 2015).

6.2 | miR-192

miR-192 is involved in cell proliferation via p53, P52, and TGFB signaling pathways. It is decreased in peripheral blood of asthmatic patients (Yamamoto et al., 2012). Asthmatic children have lower blood miR-192 levels that may be involved in T-cell differentiation and polarization (D. Zhang, Wu, & Sun, 2018).

6.3 | miR-221

P27kip1, a target of miR-221, affects mast cells involving in the inflammation and pathogenesis of asthma. The inhibition of this miRNA reduces the permeability of inflammatory cells. This miRNA also regulates the cell cycle checkpoint in mast cells (F. Liu, Qin, Xu, Zhou, & Zhao, 2012; Qin et al., 2012). The effect of miR-21 on the cell cycle has also been documented. Increasing miR-21 and reducing PTEN in asthma can activate the PI3K/AKT pathway resulting in the increase of the cell proliferation and cell migration. PTEN is located on the chromosome 10 and has a central role in asthma (Y. Liu, Yang et al., 2015).

TABLE 6 miRNAs affecting Th1/Th2 cells

Th1/Th2	miRNAs	Target Gene	Alternation	Sample	Study population	Ref. (PubMed IDs)
Th2	miR-18a	*TGF-BR2*	Down	Lung (bronchial epithelial cells)	Patients with asthma (15) versus healthy control (13)	25360780
Th2	miR-27b	*TGF-BR2*	Down	Lung (bronchial epithelial cells)	Patients with asthma (15) versus healthy control (13)	25360780
Th2	miR-128	*TGF-BR2*	Down	Lung (bronchial epithelial cells)	Patients with asthma (15) versus healthy control (13)	25360780
Th2	miR-155	*TGF-BR2*	Down	Lung (bronchial epithelial cells)	Patients with asthma (15) versus healthy control (13)	25360780
Th2	miR-19b	*TGF-BR2*	Down	Lung (bronchial epithelial cells)	Patients with asthma (15) versus healthy control (13)	25360780
Th2	miR-106b	*TGF-BR2*	Down	Lung (bronchial epithelial cells)	Patients with asthma (15) versus healthy control (13)	25360780
Th2	miR-181b	*SPP1*	Down	Epithelial	Patients with asthma (8) versus healthy control (4)	27192552
Th2	miR-181b	*SPP1*	Down	Plasma	Patients with asthma (72) versus healthy control (35)	27192552
Th2	miRNA-221	*PTEN*	Up	BALF	Patients with asthma (8) versus healthy control (8)	26901347
Th2	miR-19a	*PTEN* *Socs1* *Tnfaip3*	Up	Peripheral blood (CD4 + T cells)	Steroid-using subjects with asthma (21), steroid-naive subjects with asthma (13) versus healthy control (8)	25362490
Th2	miR-181a	*NM*	Up	BALF	Patients with asthma (6) versus healthy control (6)	22580216
Th2	miR-150	*NM*	Up	BALF	Patients with asthma (6) versus healthy control (6)	22580216
Th2	miR-146a	*NM*	Up	BALF	Patients with asthma (6) versus healthy control (6)	22580216
Th2	miR-146b	*NM*	Up	BALF	Patients with asthma (6) versus healthy control (6)	22580216
Th2	miR-155	*NM*	Up	BALF	Patients with asthma (6) versus healthy control (6)	22580216
Th2	miR-146a	*NM*	Down	Blood (CD4 + T cells) and blood (CD8 + T cells)	Patients with asthma (8) versus healthy control (8)	21917308
Th2	miR-146b	*NM*	Down	Blood (CD4 + T cells) and blood (CD8 + T cells)	Patients with asthma (8) versus healthy control (8)	21917308
Th2	miR-487b	*AQP4*	Up	Lung (bronchial epithelial cells)	Patients with asthma (16) versus healthy control (16)	22679274
Th2	miR-181c	*AQP4*	Up	Lung (bronchial epithelial cells)	Patients with asthma (16) versus healthy control (16)	22679274
Th2	miR-let7f	*AQP4*	Up	Lung (bronchial epithelial cells)	Patients with asthma (16) versus healthy control (16)	22679274
Th2	miR-203	*AQP4, AHR*	Down	Lung (bronchial epithelial cells)	Patients with asthma (16) versus healthy control (16)	22679274
Th1	miR-625-5p	*ESR1*	Down	Peripheral blood	Patients with asthma (50) versus healthy control (50)	27277384
Th1	miR-22-3p	*PPARGC1B*	Down	Peripheral blood	Patients with asthma (50) versus healthy control (50)	27277384
Th1	miR-513a-5p	*CBL*	Down	Peripheral blood	Patients with asthma (50) versus healthy control (50)	27277384
Th2	miR-98	NM	Up	Peripheral blood	Patients with asthma (20) versus healthy control (20)	28760845
Th2	miRNA-145	NM	Up	Sputum	Patients with asthma (13) versus healthy control (7)	28694694
Th2	miRNA-338	NM	Up	Sputum	Patients with asthma (13) versus healthy control (7)	28694694

6.4 | miR-145 and miR-146

Kruppel-like factor 4 (KLF4) is a target for miR-145 and miR-146. KLF4 directly binds to the P21 promoter and inhibits cell cycle. However, it has been indicated that the increased expression of these miRNAs inhibit KLF4 (Y. Liu, Sun et al., 2015).

6.5 | miR-34/449 family

miR-34c-5p, miR-449a, and miR-449b-5p, members of the miR-34/449 family, have been recently recognized as a vital regulator for epithelial cells differentiation. As DLL1 and NOTCH1 are targets of these miRNAs and NOTCH1 antagonists can inhibit IL-13, it is assumed that inhibiting IL-13 by miR-34/449 can increase NOTCH1, which subsequently results in the activation, differentiation, proliferation, and enhancement of mucosal cells (Solberg et al., 2012). miR-323-3p can also inhibit SMAD2 and SMAD3 and interfere with IL-22 through TGF, STST3, and CDKN1B, to control the stage G1 of cell cycle (Kärner et al., 2017; Figure 3; Table 5).

7 | MicroRNAs: INTERACTIONS WITH Th CELLS IN ASTHMA

TGF is a target for miR-18a, miR-155, miR-27b, miR-19b, miR-106b, and miR-128, though these miRNAs can also act through NF-kB and NFAT pathways. A decrease in miR-18a, miR-155, miR-27b, miR-19b, miR-106b, or miR-128 leads to the increase in IL-6 and IL-8, cytokines that are produced by Th2 cells and can contribute to the pathogenesis of asthma (Martinez-Nunez et al., 2014). In addition, secreted phospho protein 1 (SSP1) is an extracellular protein target for miR-181b. A decrease in miR-181b is associated with an increase in SPP1. SSP1 can increase the expression of IL-13 and the number of eosinophils through IL-1b and chemokine ligand 1 (ccl1), and accordingly, contributes to asthma and lung fibrosis pathogenesis (Huo et al., 2016). miRNA-221 is increased in prostate, breast, and bladder cancer, and has been identified as an early diagnostic cancer biomarker. A decrease in miRNA-221 through the PTEN pathway can increase IL-4 that, in turn, increases the IgE levels, differentiates towards Th2 cells, and promotes asthma pathogenesis (Fan et al., 2016; Zhou et al., 2016). In addition to cell cycle, miR-19a also affects the differentiation of Th2 cells. It specifically targets PTEN, Socs1, and Tnfaip3 pathways. PTEN pathway suppresses PI3K and promotes T cells differentiation, Socs1 pathway suppresses IL-12 and IFN-γ due to JAK-STAT, and Tnfaip3 pathway produces A20 protein (as a negative regulator of NF-kB) that its inhibition leads to the increase of IL-2 (Simpson et al., 2014). A study on asthma indicated that the increase of miR-181a, miR-146a, miR-146b, miR-150, and miR-155 could trigger T cell activation, IL-4 elevation, lymphocyte, and eosinophil entry to lungs as well as Th2 cells differentiation, all of which contribute to asthma pathogenesis (Feng, Shi, Qiu, & Peng, 2012). Another study has also demonstrated the effect of miR-145 and miR-146 on Th2 cells differentiation (Tsitsiou et al., 2012). Another study on miR-487b, miR-181c, miR-let7f, and miR-203 demonstrated Aquaporin 4 (AQP4) and Aryl hydrocarbon receptor (AHR) as their targets. AQP4 and AHR are involved in Th2 differentiation and an increase in AQP4 can lead to an increase in IL-8 and asthma promotion (Jardim, Dailey, Silbajoris, & Diaz-Sanchez, 2012). In addition, the decrease in miR-625-5p, miR-22-3p, and miR-513a-5p has been reported in asthma patients, which targets estrogen receptor 1 (ESR1), peroxisome proliferator-activated receptor gamma-coactivator 1 beta (PPARGC1B), and Cbl proto-oncogene, and E3 ubiquitin protein ligase (CBL), respectively. miR-513a-5p affects CBL to block EGFR and spleen tyrosine kinase (SYK) and alters the signaling pathway. Moreover, miR-625-5p and miR-22-3p affect their targets to reduce Th1 cytokines such as IL-10, IL-12, and IFN-γ through PI3K and NF-kB pathways (Dong et al., 2016; Figure 4; Table 6).

8 | CONCLUSION

Due to the lack of complete understanding of asthma pathogenicity mechanisms, further studies on miRNAs involvement in asthma pathogenicity are required. It seems that miRNAs may be potential asthma diagnostic and therapeutic biomarkers in the near future.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

AUTHOR CONTRIBUTIONS

SRM, SAJ, JS, and AA designed, performed the systematic search, and interpreted the results. All authors contributed in writing the manuscript. SRM, JS, and SAJ designed the tables and figures.

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