Chapter

The Blood Biomarkers of Asthma

Chen Hao, Cui Yubao and Zhu Rongfei

Abstract

Asthma was a chronic inflammatory airway disease which characterized by complex pathogenesis, various clinical manifestations and severity. Blood biomarkers have been used to evaluate the severity of the disease, predict the efficacy and prognosis. Currently, some incredible progress in most of the research on biomarkers for asthma have achieved, including cell, antibodies, cytokines, chemokines, proteins and non-coding RNAs. We reviewed the application of these biomarkers in diagnosis, treatment, prognosis monitoring and phenotypic identification of asthma, in order to improve clinicians' understanding of asthma biomarkers.

Keywords: biomarker, asthma, cell, antibodies, cytokines, chemokines, proteins, non-coding RNAs

1. Introduction

Asthma was a chronic inflammatory airway disease which characterized by complex pathogenesis, various clinical manifestations and severity. With an increasing prevalence, asthma affecting an estimated 358 million people worldwide [1]. According to the recent epidemiological data in China, there were 45.7 million adult patients with asthma and the total prevalence rate was 4.2% [2]. The cumulative prevalence among children under 14 years of age was 3.02%[3]. The high prevalence and different clinical manifestations lead to various treatment of asthma. Therefore, it was very important to determine the classification and specific markers for the management of asthma.

Francisaca et al. have proposed to classify asthma phenotypes into allergic asthma, eosinophilic asthma, obese asthma, persistent asthma, symptomatic asthma, positive bronchial provocation test with asthma symptoms, positive bronchial provocation test with no asthma symptoms, and negative bronchial provocation test with asthma symptoms [4]. This classification method mainly focuses on the presentation of symptoms and does not guide the precise treatment of asthma patients. Identifying the phenotype of asthma according to the molecular mechanism can solve this problem to a certain extent.

Asthma can be classified into T2 and non-T2 asthma according to the molecular mechanism of airway inflammation. The former was mainly composed of eosinophils (EOS), mast cell (MC), dendritic cells (DC), and Type 2 innate lymphoid cells (ILC2), which secrete immunoglobulin E (IgE), Interleukin-4 (IL-4), IL-5, IL-13, IL-33, prostaglandin D2, thymic stromal lymphopoietin (TSLP) and other antibodies and inflammatory factors. Non-T2 asthma was involved in the secretion of cytokines

such as IL-1, IL-6, IL-17, CXCL-1 and 8, interferon-γ (IFN-γ), and tumor necrosis factor (TNF)-α by inflammatory cells such as neutrophils (NEU) [5]. A number of biomarkers have been identified in broncho alveolar lavage (BAL), peripheral blood, induced sputum, and bronchial biopsy tissue and etc. According to the pathogenesis of different asthma phenotypes, among these samples, peripheral blood can be easily obtained in clinic practice. Thus, we investigate potential biomarkers in peripheral blood for asthma patients, in order to enhance the management and treatment of asthma.

2. Blood biomarkers of asthma

2.1 Cellular biomarkers

EOS in peripheral blood were considered as an important biomarker for asthma, and can predict the treatment response [6]. A small prospective cohort study of hospitalized infants with asthma demonstrated that elevated EOS in convalescence can predict an increased risk of asthma in the future [7, 8] Neutrophils (NEU) in peripheral blood can assess asthma control and prognosis, the counts of NEU over 5000/ul means that asthma symptoms were poorly controlled and likely to get worse [9]. Basophils contains cytoplasmic secretory granules, and was consisted by proteoglycans and histamine [10]. Basophil activation test (BAT) was a useful method for marking CD63 and CD203c, which were the most common surface markers of basophil activation. The detection of CD63 and CD203c implied that basophil degranulation and may led to histamine release, which provide crucial information for the diagnosis of allergic asthma [11].

Mast cell (MC) also played an important role in allergic inflammation. A study suggested that interactions between mast cells and airway smooth muscle cells were critical for the development of the disordered airway physiology in asthma [12]. Therefore, mast cell activation test can be used as a diagnostic method of asthma.

Innate lymphoid cells (ILC), which was different from T cells and B cells, are located on the mucosal surface of the intestine and played an important role in enhancing the immune response, maintaining mucosal integrity and promoting the formation of lymphoid organs. According to the cytokine expression profile, ILC can be divided into three groups: ILC1, ILC2 and ILC3, among which ILC2 can produce a large number of T2 cytokines, such as IL-5 and IL-13 [13], which can promote EOS and airway hyperresponsiveness (AHR), led to exacerbating the symptoms of asthma. The level of activated ILC2s in blood, bronchoalveolar lavage fluid (BALF), and sputum of asthmatic patients were increasing compared with healthy controls [14]. Thus, ILC2 can be regard as an important biomarker for the assessment of asthma.

T helper (Th2) and non Th2 were phenotypes of asthma and have been determined by CD4+T cells [15]. Th2 asthma was characterized by elevated EOS and high levels of interleukin (IL)-4, IL-5 and IL-13 [16]. In contrast, non Th2 asthma was characterized by NEU infiltration and high levels of IFN-γ and IL-17 [15]. Since the progression pattern and treatment plan of asthma depend on the differentiation of CD4+T cells, clarifying the biological role of CD4+T cells in the pathogenesis of asthma was very important to develop effective treatment and predict the prognosis of asthma patients [17].

Forkhead box P3 (Foxp3)+ regulatory T (Treg) cells were a special subgroup of CD4+T cells, which played a key role in maintaining immune tolerance and inhibiting

immune response to antigens [18]. In patients with severe asthma, the number of Treg cells in blood, BALF and sputum was decreased [19, 20], which concluded that Treg cells can be used to assess asthma severity.

Macrophages were account for about 70% of the immune cells in the asllergic asthma, and played an important role in airway inflammation [20]. A study has shown that the impaired function of alveolar macrophages always be presented in children with poorly controlled asthma which were, characterized by decreased phagocytosis and increased apoptosis [21]. Therefore, macrophages also play an important role in assessment of asthma administration.

2.2 Antibody biomarkers

Mucosal IgA neutralizes bacteria and viruses by interfering with epithelial adhesion and improving the characteristics of mucus capture and antigen removal [22]. One report have shown that infants with low IgA levels have more common asthma and more severe allergic symptoms. In addition, infants born to allergic parents were more prone to deficiency of salivary IgA [23]. Another report shows that serum IgA levels in adult patients with asthma are associated with asthma severity [24]. Therefore, IgA level has certain guiding significance for the severity of asthma symptoms.

The amount of total IgE (tIgE) in serum and the presence of allergen-specific IgE(sIgE) antibodies are important biomarkers to assess the phenotype and symptoms of asthma patients. The level of sIgE in serum may also be helpful to predict persistent wheezing. Furthermore, tIgE was associated with asthma and can be considered as a supplementary indicator for the severity of asthma [25]. One study investigated that in the HDM sensitized children, the ratio of sIgG to sIgE in asthma children was significantly lower than that of non-asthma children, and was the lowest among the children with the most severe asthmatic symptoms, which speculated that sIgG may play a certain inhibitory role in the pathogenesis of asthma [26]. Thus, sIgG/sIgE has been used as a biomarker for more accurate evaluation of asthma than single sIgE.

2.3 Cytokine markers

Allergic asthma was driven by T-helper type 2 (Th2) cells, inducing the production of inflammatory cytokines such as IL-4, IL-5 and IL-13. IL-4 and IL-13 are key drivers of a variety of atopic diseases [27]. In addition to Th2 cells, other lymphocytes include γδT cell subsets, natural killer T (NKT) cells, T follicular helper cells (Tfh) cells and type 2 innate lymphoid cells (ILC2s) can also produce IL-4 and/or IL-13 [28]. IL-4 was a differentiation factor that polarizes naive CD4+T cells to Th2 phenotype [29]. It was essential in inducing local Th2 response and the development of pulmonary eosinophilic inflammation [30], but didn't have direct effect on mucus production [31].

IL-5 can increase expression of C-C chemokine receptor 3 (CCR3) by mature EOS [32], it was also conducive to the recruitment and activation of EOS in asthma patients [33]. Although the activation of Th2 cells in allergic asthma lead to the increase of some cytokines, such as IL-13, IL-4, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [34], the predominant cytokine associated with antigen-induced eosinophilic inflammation still was IL-5 [35]. In brief, IL-5 palyed an important role in the evaluation of eosinophilic inflammation in asthma.

IL-13 can induce B cells to synthesize IgG4 and IgE, which provided pivotal signal in allergic disease [36]. As aT2 inflammatory cytokins, IL-13 can be produced by CD4+T, EOS, MC, basophils, and NKT [37]. IL-13 had various roles in asthma, for example, it can switched antibody synthesis of plasma cell and produced IgE, and promoted the migration of EOS to the lungs. Because of the EOS synthesis and the up-regulation of adhesion molecules bound to EOS, goblet cell proliferation and mucus production would increased, which lead to increased sputum and AHR [38].

Asthma patients have a higher levels of serum IL-4, IL-5 and IL-13 compared with healthy controls these cytokines were also increased in acute asthma [39]. A clinical study has shown that blocking both IL-4 and IL-13 signaling can significantly reduce the exacerbation of severe asthma [40], and after anti-IL-5 treatment, 83% of patients with severe asthma had a favorable responses [41].

CD4+T cells, particularly activated Th2 cells, have been found to represent a major cellular source for IL-31 [42]. Polymorphisms in IL-31 is associated with IgE production in asthma patients [43]. at the same time, IL-31 promoted the occurrence of chemokines and pro-inflammatory cytokines in human bronchial epithelial cells (HBECs), and could lead to a Th2-dominant inflammation in asthma [44]. The levels of IL-31 in serum and BALF were increased in asthma patients and IL-31 also was positively correlated with Th2 cytokines (IL-5, IL-13, TSLP) and the severity of asthma [45].

Th17 related cytokines such as IL-17A, IL-17F, IL-21 and IL-22 were secreted by Th17 cells. In the mice model of allergic asthma, the impairment of IL-17R signal delayed the recruitment of neutrophils to the alveolar cavity [46]. IL-17 also activated airway NEU by increasing elastase and myeloperoxidase activities, and promoted exacerbation of asthma [46]. It has shown that IL-17 may play an indirect role in airway remodeling of asthma, the increased concentration of IL-17 in PBMCs and plasma always implied that the asthmatic symptoms prone to more severe [47, 48]

IL-9 can be produced by a variety of cells including Th2 cells, Th9 cells, EOS and NEU [16], and Th9 cells were the main source of IL-9. Th9 cells promoted mast cell accumulation and activation in mice model of allergic pulmonary inflammation [49], while IL-9 can inhibit the production of IFN-γ and promote secretion of mucus and IgE [50, 51]. A study have found that both Th9 cell and IL-9 of peripheral blood increased in allergic asthma patients [52],which means that IL-9 can be regarded as a biomarker of asthma.

IL-25, IL-33 and TSLP derived from airway epithelium and played an important role in the pathogenesis of asthma [53]. Among them, IL-25 not only targeted innate immune cells to produce Th2 cytokines, but also guided the translation of naive Th cells to Th2 cells [54]. Overexpression of IL-25 in lung epithelium induced epithelial cell proliferation, increased mucus secretion, airway infiltration of eosinophils and macrophages, and up-regulated the chemokines related to Th2 cells [55]. Plasma IL-25 levels were also associated with epithelial IL-25 expression and may be useful for predicting responses to asthma therapy [56].

Genome wide and candidate gene association studies have identified that common single nucleotide polymorphisms (SNPs) in IL-33 and IL-1 receptor like 1 (IL-1RL1) loci associated with asthma, especially pediatric asthma [57]. IL-33 activated a large number of immune cells and structural cells by binding to IL-33 receptor complex, which can promote occurrence and exacerbation of asthma [58]. The IL-33/ST2 (suppression of tumorigenicity 2) axis triggered the release of several proinflammatory mediators, such as chemokines and cytokines, and induced systemic T2 inflammation in vivo [59]. IL-33/ST2 pathway also contributed to allergen induced airway

inflammation and hyperresponsiveness [60]. Compared with healthy individuals, the concentration of IL-33 in plasma was higher in asthma patients [61].

To some extent, AHR, mucus overproduction and airway remodeling, were considered to be drived by TSLP through its downstream proinflammatory effect [62]. Stimulation of basophils with TSLP can increase the percentage of IL-25 receptor (IL-17RB) and ST2, suggesting that TSLP can enhance the responsiveness of basophils to other alarmin cytokines [63]. The levels of plasma TSLP in asthma patients were higher than that in healthy controls, Airway submucosal EOS would be reduced by blocking TSLP in patients with moderate-to-severe uncontrolled asthma compared with placebo [64].

2.4 Chemokine markers

Eotaxin, as a ESO chemokine, can attract EOS to the site of allergic inflammation by stimulating CCR3. Eotaxin played a role in the early stage of Th2 lymphocyte recruitment [65], and the concentration of airway eotaxin was related to the sensitivity of asthmatic airway [66]. A study has demonstrated that there was a direct relationship between asthma diagnosis and eotaxin, and the levels of plasma eotaxin were negatively correlated with pulmonary function [66].

CCR2 was expressed in monocytes and T lymphocytes [67]. CCR2 mediated release of monocyte precursors leads to the increase of lung dendritic cells (DC) in allergic airway inflammation [68]. A study showed that monocytes may modulate the inflammatory response in asthma [69]. In a mouse asthma model, CCL2/CCR2-dependent recruitment of Th17 cells to the lung promoted airway inflammation [70]. In a monkey asthma model, Neutralization of CCR2 reduced bronchial hyperreactivity and weakened the accumulation of macrophages and eosinophils in BALF [71]. Therefore, the elevated CCR2 was a diagnostic biomarker for asthma.

CCR3 was mainly expressed on EOS, and can also be detected on basophils and T cells [67]. CCR3 showed sequence homology in many species, including humans, mice and guinea pigs. Its expression was limited to cells involved in allergic inflammation [72]. MicroRNA-30a-3p (miR-30a-3p)can inhibit CCR3 signaling pathway, reduce the secretion of sIgE against ovalbumin (OVA), eotaxin, IL-5 and IL-4 [73]. The expression of CCR3 on the surface of PBMCs was positively correlated with severity of asthma [74]. Inhibition of CCR3 blocks eosinophil recruitment into the blood, lungs and airways and prevents AHR in a mouse asthma model [75].

CCR5 was expressed in T lymphocytes and macrophages [67]. The increased CCR5 lead to EOS accumulation and airway remodeling in asthma patients [76]. Compared with healthy subjects, the expression of CCR5 in peripheral blood lymphocytes increased in asthma patients, and inhibition of CCR5 was a feasible method for blocking AHR [77, 78].

Thymus and activation-regulated chemokine (TARC) was produced by DC, endothelial cells, keratinocytes, bronchial epithelial cells and fibroblasts [79]. As chemokine related T2 inflammation, TARC contributed to the activation of EOS and MC driven by Th2 [80]. A series of studies concluded that the TARC concentration of asthma children increased in plasma [81], and after treatment of systemic corticosteroid (CS), the concentration decreased. In addition, the levels of TARC were negatively correlated with indicator of lung function such as peak expiratory flow rates in asthma patients [82].

Monocyte chemotactic protein-4 (MCP-4) was a potential chemical attractant not only for EOS, but also for monocytes, lymphocytes and basophils [83]. It have been

confirmed that MCP-4 can induce histamine release and activation of the EOS [74]. Plasma MCP-4 was higher in patients with acute asthma than in those with chronic stable asthma [83], which implied that MCP-4 was correlated with exacerbation of asthma.

2.5 Protein biomarkers

Heat shock protein 72 (HSP-72) belongs to the Hsp70 family of heat shock proteins. It regulated protein expression during conditions of cell stress and acted as a protective factor by preventing abnormal protein aggregation, thus helping to refold damaged proteins, which was related to inflammation and obesity. Obesity was considered to be a risk factor for asthma, and serum and urine Hsp72 levels were significantly elevated in patients with severe asthma and obesity-related asthma. Hsp72 also was an independent predictor of asthma severity and could be used as a simple, non-invasive biomarker for predicting and monitoring asthma severity in obese asthma patients [84].

Eosinophil cationic protein (ECP) was secreted by activated eosinophil and is a specific marker of EOS. Serum ECP levels were significantly increased in children and adults with allergic asthma during acute stage. ECP, as a strong alkali-toxic protein, had strong effects on airway and nasal epithelium and had been associated with AHR, eosinophilic chronic sinusitis, aspirin-aggravated respiratory disease, and recurrent wheezing [85]. Elevated ECP concentrations in serum reflected EOS activation and were associated with asthma severity and allergen sensitization. In children with acute asthma, serum ECP was a more sensitive biomarker of asthma severity than blood EOS [86].

Periostein was a matrix protein that expressed in fibroblasts and epithelial cells, which was involved in a variety of biological processes, such as cell proliferation, cell invasion, and angiogenesis. In asthma patients, periostein associated with EOS migration and promoted production Th2 cytokines such as IL-4 and IL-13, lead to chronic allergic inflammation. It was found that the best cut-off value of sputum periostein which distinguished mild and moderate to severe asthma was 528.25 ng/mL [87]. Serum periostein was associated with AHR, blood EOS counts and FeNO in asthma children. The level of sputum periosteins was positively correlated with age, asthma course and sputum EOS increase, which was a surrogate biomarker and therapeutic target of severe eosinophil asthma.

High mobility group protein B1 (HMGB1) was a protein that specifically binds to nucleosome DNA junction region, it can enhance nucleosome stability and transcription factor interaction. In asthma, acute respiratory distress syndrome (ARDS), cystic fibrosis, lung cancer and other lung diseases, HMGB1 induced the production of pro-inflammatory cytokines and exacerbated airway inflammation, and anti-HMGB1 can reduce the pathological features of asthma [88].

Serum chitinase-like protein YKL-40, a member of the chitinase family, might be involved in the development of fibrosis and airway remodeling. YKL-40 was involved in the pathogenesis of asthma by inducing IL-8 in the epithelium and was considered as one of the biomarkers of asthma patients [89]. In addition, YKL-40 also indicated neutrophil inflammation in asthma and was associated with asthma severity. Moreover, YKL-40 was significantly negatively correlated with lung function [90].

CD14 was a marker of activation of monocytes or macrophages, which existed in membrane-bound form (mCD14) and soluble form (sCD14) and had a positive effect on the balance between Th1 and Th2 cytokines. Soluble CD14(sCD14) played

an important role in proliferation and activation of T and B cell. The level of sCD14 in asthma patients was significantly higher in the acute stage than in the convalescence stage. There was a significant correlation between plasma sCD14 level and the severity of asthma, lung function, asthma symptoms and signs in adults, and there was a negative correlation between sCD14 level and asthma severity [91]. Therefore, plasma sCD14 levels may be a potential biomarker for predicting asthma severity in adults.

Serum arginase I levels were significantly elevated in asthmatic patients compared with healthy controls and C-reactive protein (CRP) was a common inflammatory marker for assessing systemic inflammation. In asthma patients, serum high sensitivity CRP (HS-CRP) levels were elevated and associated with respiratory symptoms and airway inflammation. Serum arginase I level was positively correlated with HS-CRP and negatively correlated with IgE in asthma patients. Elevated serum arginase I levels might be serve as a biomarker of airway inflammation in asthma [92].

The OX40 ligand (OX40L,) and its receptor OX40 were members of the tumor necrosis factor (TNF) receptor superfamily. Serum OX40L was positively correlated with serum IgE, IL-6, percentage of EOS and NEU, TSLP, and negatively correlated with asthma severity and lung function. Inhaled corticosteroid (ICS) treatment can reduce serum OX40L levels, and the reduction of serum OX40L was more significant in steroid-sensitive asthma than in steroid-resistant asthma. High serum OX40L can be used as a biomarker for identifying glucocorticoid resistance in asthmatic patients. Changes in OX40L levels also reflect response to ICS treatment [93].

2.6 Non-coding RNA biomarkers

MicroRNAs (miRNAs) were small non-coding RNA molecules that were considered to be one of the basic regulatory mechanisms of gene expression. They were involved in many biological processes, such as signal transduction, cell proliferation and differentiation, apoptosis and stress response [94]. Sufficient evidence have been suggested that miRNA play a role in several key points of asthma, including the diagnosis of asthma, disease severity, and response to treatment [95].

Serum miRNA-21 and miRNA-155 levels were significantly elevated in asthma patients compared with healthy controls. The expression level of miRNA21 in serum of asthma patients was significantly positively correlated with the level of IL-4. In addition, compared with steroid-sensitive children, miRNA-21 was significantly elevated in untreated and steroid-resistant children, and miRNA-21 could be a promising biomarker for diagnosis and response to inhaled corticosteroid therapy [96].

MiR-20a-5p was significantly down-regulated in the lungs and OVA-stimulated cells of mouse models of OVA induced asthma, and miR-20a-5p may be a promising biomarker and therapeutic target during asthma progression by targeting ATG7's involvement in autophagy-induced apoptosis, fibrosis and inflammation [97]. MiR-582-5p was strongly upregulated in nasal epithelial cells of children with severe acute asthma [98]. MiR-145-5p was associated with lung function in children with asthma and also increased proliferation of airway smooth muscle cell. This suggests that the decreased expression of miR-145-5p was a risk factor for early decline in long-term lung function [99]. MiR-124 contributed to the development and maintenance of anti-inflammatory phenotypes of asthmatic lung macrophages, and was negatively correlated with the risk of exacerbation, severity and inflammation in asthma patients [100].

MiRNA-155, a key regulator of type 2 innate lymphocytes in a mouse model of allergic airway inflammation, was elevated in serum samples from allergic asthma

patients compared with non-allergic asthma patients and healthy individuals. Expression of miR-155 was altered by allergic stimulation or glucocorticoid treatment, which can be used as biomarkers for steroids resistance/neutrophilic asthma [101]. MiRNA-223 was significantly upregulated in patients with moderate asthma compared with healthy controls, and no significant difference in miR-223 expression was found between patients with severe asthma and healthy controls, which could serve as a potential biomarker for the diagnosis of moderate asthma [102]. The level of miR-192 in asthma children was lower than that in healthy children, and miR-192 blocked the activation pathway of Tfh cells by targeting CXCR5 [103]. Serum miRNA-1165-3P levels were significantly elevated in asthma patients compared to healthy controls. In addition, Serum miR-1165-3p levels were also significantly elevated in patients with allergic rhinitis (AR) or allergic bronchopulmonary aspergillosis (ABPA), suggesting that serum miR-1165-3p may be used as a non-invasive biomarker to help diagnose and characterize allergic asthma [104]. MiRNA-3934 levels in peripheral blood mononuclear cells of asthma patients were significantly decreased, and miRNA-3934 levels in PBMCs could distinguish asthma patients, especially severe asthma patients from control group. MiRNA-3934 levels in PBMCs of asthma patients were negatively correlated with serum IL-6, IL-8 and IL-33 levels, respectively, which might also be a potential diagnostic biomarker for asthma [105]. In addition, upregulation of MiR-1165-3p reduced AHR and airway inflammation by directly targeting IL-13. MiR-185-5p was involved in calcium signaling by targeting NFAT and CaMKII proteins in cardiomyocytes and may play a role in muscle cell hyperplasia, proliferation and cell contraction in asthma, suggesting that these candidate biomarkers play a role in the pathogenesis of asthma [106]. Overexpression of MiRNA-126 in acute asthma was associated with signs of immune imbalance and can predicted disease severity, suggesting that it can be used as a potential serologic marker for the diagnosis and evaluation of asthma [107].

Long non-coding RNA (lncRNAs) affected the regulation of immune response, airway inflammation and other pathological processes related to asthma. PTTG3P was highly expressed in peripheral blood of children with asthma and promoted the progression of childhood asthma by targeting miR-192-3p/CCNB1 axis and may serve as a potential diagnostic and therapeutic biomarker for childhood asthma [108]. LncRNA NEAT1 was up-regulated in patients with asthma exacerbation compared with healthy controls and patients with asthma in remission stage, which was positively correlated with the severity of asthma exacerbation, TNF-α, IL-1β and IL-17, but negatively correlated with predicted IL-10, FEV1/FVC and FEV1%. Circulating lncRNA NEAT1 may be a novel biomarker for increased risk and severity of asthma exacerbations [100]. LncRNA-ANRIL/MiR-125a axis was upregulated in patients with acute asthma compared with those in remission and healthy subjects, and the LncRNA ANRIL/MiR-125a axis had good predictive value for the risk of bronchial asthma disease progression [109]. Compared with non-severe asthma patients, the expression of lncRNA GAS5 in PBMCs of severe asthma patients was increased. After treatment with CS in vitro, the expression of GAS5 was down-regulated in severe asthma patients, while up-regulated in non-severe asthma patients, highlighting the potential role of GAS5 as a biomarker for the diagnosis of severe asthma patients [110]. Compared with the healthy control group, the level of lncRNA-MEG3 in CD4+T cells of asthma patients was significantly increased, and the degree of Treg/Th17 imbalance was correlated with the severity of asthma mice symptoms. LncRNA-MEG3 can be used as a competitive endogenous RNA to inhibit the level of miRNA-17, miRNA-17 inhibits Th17 expression by directly targeting nuclear orphan receptor γ

T (RORγ T). Thus affecting Treg/Th17 balance in asthma, monitoring lncrNA-MEG3 in asthma patients can be used to judge the course of disease or recovery of patients [111]. The level of lnc-BAZ2B in children with allergic asthma was significantly higher than that in healthy children. Lnc-BAZ2B can aggravate allergen-induced pulmonary allergic inflammation by promoting the activation of M2 macrophages, which is positively correlated with the severity of asthma and blood eosinophil count. Thus, Lnc-BAZ2B plays a key role in exacerbating the progression of allergic asthma and may serve as a potential diagnostic marker for childhood asthma [112].

3. Conclusion

In conclusion, biomarkers were indicators of normal physiological processes, disease progression and response to treatment. Although many biomarkers for asthma have been mentioned in recent studies for the diagnosis of asthma, the identification of different phenotypes and efficacy evaluation, none of them have been approved for clinical practice so far, mainly due to their limited sensitivity and specificity. With the development of biomedicine, asthma research is moving from clinical symptoms, clinical phenotypes, lung function and medication response to genomics, proteomics, epigenetics, etc. More key molecules and biomarkers will be discovered in the future. Combined detection of multiple markers can more comprehensively analyze the patient's condition, thus providing more valuable clinical information for the diagnosis, classification and treatment of asthma, and ultimately achieving accurate diagnosis and treatment of asthma patients.

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