Th17 Immunity in Patients with Allergic Asthma

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Key Words
T helper cells \cdot Interleukin \cdot Allergic asthma

Abstract
Background: Allergic asthma is an inflammatory disease regulated by the T helper (Th) cells. The Th1/Th2 imbalance has been well documented in the pathogenesis of allergic asthma. Recently, Th17 cells have been found to participate in the development of allergic asthma in animals. However, whether Th17 immunity contributes to the systemic immune responses in allergic asthmatic patients is unclear. Methods: Peripheral blood mononuclear cells were isolated from allergic asthmatics (n = 29) and healthy controls (n = 12). The frequencies of Th1, Th2 and Th17 cells were analyzed by flow cytometry. The related cytokine (IFN-\textgamma, IL-4, IL-17, IL-22, IL-23 and IL-25) concentrations in plasma and culture supernatants were measured by enzyme-linked immunosorbent assay and Luminex. The level of retinoic acid-related orphan receptor \gamma-t (ROR\gamma-t), a key transcription factor controlling Th17 differentiation, was examined by real-time quantitative polymerase chain reaction. Results: The percentages of Th2 and Th17 cells as well as the concentrations of Th2- and Th17-related cytokines were higher in allergic asthmatics than those in healthy controls; some patients were even treated with inhaled glucocorticoid. The percentages of Th17 cells as well as the plasma concentrations of IL-17 and IL-22 tended to increase with the severity of the disease, while the IL-25 level was elevated in mild patients. A parallel elevation of IL-17 and IL-23 concentrations and an increase in ROR\gamma-t level were found in allergic asthmatics. Conclusion: Our results suggest that besides predominant Th2 immunity, abnormal Th17 immunity may be also involved in the pathogenesis of allergic asthma.

Introduction
Allergic asthma is a complex and chronic inflammatory airway disease in which many cells and cellular elements play a role, such as mast cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells. The imbalance of T helper cells (Th) 1/Th2 immunity plays an important role in the pathogenesis of allergic asthma\cite{1}. Th17, a T cell lineage distinct from Th1 and Th2 cells, has been recognized as a novel pro-inflammatory CD4+ T effector cell\cite{2, 3}. Th17 cells, characterized by the secretion of IL-17A (also called IL-17), IL-17F, IL-22 and other cytokines, can induce autoimmunity by promoting tissue inflammation and mobilizing innate immunity\cite{4}. Recent studies have suggested that Th17 cells and Th17 cytokines were involved in the pathogenesis of allergic asthma. Research on mice showed that IL-17 could trigger lung inflammation by stimulating innate immunity and induce neutrophilic airway inflammation.
IL-22, an IL-10 family cytokine member that was recently discovered to be produced by Th17 cells, is strongly linked to chronic inflammation. Both IL-17 and IL-22 regulate CXCL chemokines and granulocyte colony-stimulating factor production in the lung [6, 7]. IL-25, initially described as a Th2-derived cytokine, is now recognized as another IL-17 family member. In mice, systemic overexpression or administration of IL-25 into the lung led to a Th2 immune response in local tissue and a lung with pathological changes which were similar to those in allergic asthmatics [8, 9]. These data suggested that IL-25 was capable of amplifying allergic inflammatory responses.

At present, all related reports implicated that Th17 immunity might play a critical role in the pathogenesis of allergic asthma, although these studies just focused on abnormal Th17 immunity in local sites or in animal models, a detailed assessment of Th17 immunity in the systemic allergic reaction and immune responses in allergic asthmatic patients has not been fully reported. In the present study, we investigated the frequencies of Th1, Th2 and Th17 cells and the concentrations of their related cytokines (IFN-γ, IL-4, IL-17, IL-22, IL-23 and IL-25) in peripheral blood from allergic asthmatics and healthy controls. Then we analyzed whether the number of Th17 cells and the concentrations of Th17-related cytokines (IL-17, IL-22 and IL-25) were related with the severity of allergic asthma. Furthermore, the expression of transcription factor retinoic acid-related orphan receptor γt (RORγt) was also assayed. Our results demonstrated an abnormal systemic Th17 immunity in allergic asthmatics, which may participate in the pathogenesis of allergic asthma.

**Subjects and Methods**

**Subjects**

Twenty-nine patients with allergic asthma (17 women, 12 men) were enrolled, selected from outpatients and inpatients of the Renmin Hospital and the Zhongnan Hospital of Wuhan University. Pulmonary functions were assessed by spirometry according to American Thoracic Society standards [10]. Asthma severity was evaluated on the basis of the Global Initiative for Asthma criteria [11]. And asthma subjects were subdivided into 3 groups: mild (mild intermittent, n = 6; mild persistent, n = 7), moderate (n = 7) and severe (n = 9) asthmatics. All patients were permitted to be treated with inhaled glucocorticoid but not systemic steroids during 4 weeks prior to the study. Among the asthmatics, 10 patients were treated with inhaled glucocorticoid: 500 μg/day fluticasone or equivalent (mild = 3, moderate = 3, severe = 4). All patients had a positive skin prick test, defined as a >5-mm diameter skin wheal response to at least 1 of the 10 common allergens (Dermatophagoides pteronyssinus, D. farinae, mixed grass pollen, mixed tree pollen, dog hair, feather, cat fur, fluffed cotton, cockroach and Alternaria). Twelve sex- and age-matched healthy volunteers (7 women, 5 men) were recruited as healthy controls who had normal spirometry tests. Both groups were chosen on the basis of: (1) being nonsmokers; (2) having no other allergic symptoms, no history of upper or lower airway diseases 2 months before the study, and no chronic heart and pulmonary diseases; (3) having not received immunotherapy in the previous 5 years, having not received oral or intravenous steroids in the previous 4 weeks, but allowing to receive inhaled steroids, having not received theophylline, long-acting β2-agonists, leukotriene antagonists or antihistamines in the previous 2 months before the study. For all subject characteristics see table 1. All subjects were fully informed about the purpose and nature of the studies, which were approved by the medical ethics committee of Renmin Hospital and Zhongnan Hospital.

**Cell Separation**

Twelve milliliters of peripheral blood was obtained from allergic asthmatics and healthy controls. Blood was heparinized and 1:2 diluted with phosphate-buffered saline (PBS), then layered on Lymphoprep (d = 1.077 mg/ml; Nycomed) and centrifuged at 2,000 rpm for 20 min at room temperature. Peripheral blood mononuclear cells (PBMCs) were collected and washed twice with PBS. Plasma samples were collected and preserved at −20°C for the measurement of cytokines by ELISA.

**Cell Culture**

PBMCs were re-suspended in RPMI 1640 medium (Sigma) containing 1-glutamine. HEPES buffer and 10% fetal calf serum (R10) to a concentration of 1 × 10^6 cells/ml. Cells were activated with 50 ng/ml phorbol-12-myristate-13-acetate (PMA; Sigma) and 250 ng/ml ionomycin (Sigma) for 4 h at 37°C in a 5% CO₂ atmosphere, then stimulated for additional 2 h in the presence of 1 μg/ml Brefeldin A (Fluca). Cells were harvested for intracellular staining and real-time quantitative PCR (RT-PCR) analysis. The culture supernatants before and after treatment were collected and preserved at −20°C for ELISA.

**Surface Antigen and Intracellular Cytokine Staining**

Cytokine-producing cells were sorted by surface antigen and intracellular cytokine staining using flow cytometry. CD3+CD8− cells, but not CD3+CD4+ cells, were defined as Th cells, due to the downregulation of surface CD4 molecules after stimulation with PMA and ionomycin. Cells were incubated with PE-cy5-labeled anti-human CD3 and FITC-labeled anti-human CD8 (eBioscience) for 30 min at 4°C in the dark. After washing, cells were fixed with Fixation Solution (eBioscience) and incubated for 20 min at room temperature in the dark. After permeabilization, cells were incubated with PE-labeled anti-human cytokine antibodies (IFN-γ, IL-4 and IL-17; eBioscience) for 20 min at room temperature in the dark. FITC-conjugated mouse IgG and PE-conjugated rat IgG2a (eBioscience) were used as controls. Cells were resuspended in PBS and analyzed on flow cytometer (Epics Altra; Beckman). Flow-cytometric analysis was performed with scatter gates on the lymphocyte fraction. Results are expressed as a percentage of positive cells.
Detection of Cytokines

The levels of IL-23 and IL-25 in plasma and cytokines in culture supernatants were measured by ELISA following the manufacturer’s instructions (IFN-γ, IL-4, IL-17 and IL-23 ELISA kits; R&D Systems; IL-25 ELISA kits; ADL). And the levels of IFN-γ, IL-4, IL-17 and IL-22 in plasma were detected by Luminex multiplex technology (Surexam Assay Kit). The minimal detectable concentrations were 8 pg/ml for IFN-γ and IL-23, 3.2 pg/ml for IL-4 and IL-17, and 1.0 pg/ml for IL-25. Intra- and interassay coefficients of variation for all ELISA were <5% and <10%, respectively. All samples were measured in duplicate. Undetectable values were assigned an arbitrary value of half the sensitivity limit.

RT-PCR

Total RNA was extracted from PBMCs with TRIzol (Invitrogen), then the cDNAs were synthesized using a Revertaid first-strand cDNA synthesis kit (Toyobo), following the instructions provided by the manufacturer. PCR amplifications reactions were conducted with a SYBR Green Supermix (TaKaRa) in a 20 μl reaction volume containing 200 nM primers and 5 ng cDNA. Thermal cycling was initiated with a 2-min denaturation at 95°C, followed by 34 cycles of 95°C for 30 s, 54°C for 30 s and 72°C for 30 s. All measurements were performed in duplicate. The level of RORγt mRNA expression was assessed relative to GAPDH housekeeping gene expression.

The following primer pairs were used: RORγt: 5'-ACCTCACCGAGGCACATCCCTAAC-3' (R); GAPDH: 5'-GGTGTGAACCATGAGAAGTATG-3' (R).

Statistics

All data are presented as means ± standard deviation (SD). Differences of clinical characters were analyzed by one-way analysis of variance. Differences between allergic asthmatics and healthy control were assessed by the Mann-Whitney U test. For comparison of paired data within groups, the Friedman test was used. Correlations were analyzed by Spearman nonparametric test. The difference was considered to be significant at p < 0.05 and p < 0.01, respectively). In contrast, the percentage of IFN-γ-positive CD3+CD8– T cells was lower in asthmatics than in healthy controls (p < 0.05). The percentage of Th17 cells tended to increase with the severity of allergic asthma (p < 0.05).

Frequencies of Th1, Th2 and Th17 Cells in PBMCs

Isolated PBMCs from allergic asthmatic patients and healthy controls were stimulated with PMA and ionomycin. The expression of surface antigens and intracellular cytokines was measured by flow cytometry. Representative cytometric profiles of cytokine-positive Th cells from allergic asthmatics and healthy controls are shown in figure 1a. Percentages of IL-4- and IL-17-positive CD3+CD8– T cells in PBMCs was higher in allergic asthmatics compared with those in healthy controls (p < 0.01 and p < 0.05, respectively). In contrast, the percentage of IFN-γ-positive CD3+CD8– T cells was lower in asthmatics than in healthy controls (p < 0.01; fig. 1b). The percentage of Th17 cells tended to increase with the severity of allergic asthma (p < 0.05; fig. 1c).

Th1-, Th2- and Th17-Related Cytokine Production in Plasma and Activated PBMCs from Allergic Asthmatics

The concentrations of IFN-γ, IL-4, IL-17, IL-23 and IL-25 in plasma and culture supernatants from activated PBMCs in vitro were measured by ELISA and Luminex. The levels of IL-17 in plasma were either detected at a very low level or were below the detection limit in healthy controls, so we assigned an arbitrary value of half the sensi-

Table 1. Characteristics of the subjects

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Healthy controls (n = 12)</th>
<th>Allergic asthmatics (n = 29)</th>
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<tbody>
<tr>
<td></td>
<td>33.75 ± 7.84</td>
<td>36.43 ± 8.83</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>5/7</td>
<td>6/7</td>
</tr>
<tr>
<td>Inhaled glucocorticoid</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>FEV1 pred. %</td>
<td>104.92 ± 5.19</td>
<td>88.14 ± 6.08*</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SD. FEV1 pred. % = Predicted percentage of forced expiratory volume in the first second. * p < 0.05 versus healthy controls; † p < 0.05 versus mild asthma; ‡ p < 0.05 versus all other groups.
Fig. 1. The respective frequencies of IFN-γ (Th1)-, IL-4 (Th2)- and IL-17 (Th17)-expressing cells in PBMCs from allergic asthma and healthy control subjects. PBMCs were stimulated with PMA and ionomycin for 6 h, and then stained with CD3, CD8 and the indicated intracellular cytokines. a Representative flow-cytometric profiles of the IFN-γ-, IL-4- and IL-17-producing CD3+CD8– T cells from an allergic asthma patient and a healthy control. Percentages of the indicated cells are shown in the quadrants areas. b Percentages of CD3+CD8– T cells with positive intracellular staining for IFN-γ, IL-4 and IL-17 in PBMCs from allergic asthmatics and healthy controls. The percentage of Th17 cells was associated with severity of allergic asthma. Columns represent mean values ± SD. FSC = Forward scatter. * p < 0.05 versus healthy controls; * p < 0.05 versus mild asthma; ° p < 0.05 versus all other groups.
tivity limit, 1.6 pg/ml, as levels in controls. Increased IL-4, IL-17, IL-22, IL-23 and IL-25 concentrations in plasma were observed in allergic asthma patients compared with healthy controls (p < 0.05; fig. 2b–e). Similarly, productions of these cytokines in culture supernatants of activated PBMCs were higher in asthmatics than in healthy controls (table 2). There were no differences in the expression of IFN-γ/H9253 and IL-25 between the 2 groups (p > 0.05; fig. 2a and f). However, the ratio of IFN-γ/H9253/IL-4 in plasma as well as in supernatants of activated PBMCs was lower in allergic asthmatics than in healthy controls (p < 0.05; fig. 2g; table 2).

**Plasma Concentrations of Th17-Related Cytokines Tended to Enhance with the Severity of the Disease**

We then analyzed the concentrations of Th17-related cytokines (IL-17, IL-22 and IL-25) in both plasma and activated PBMCs from allergic asthmatics with different severity. The results revealed that the concentration of IL-17 and IL-22 in plasma was consistently increased with the severity of asthma (p < 0.05; fig. 3). Although there was no difference in concentration of IL-25 in plasma between asthma patients and healthy controls, after separating patients according to severity, there was a significant increase in the amount of IL-25 in mild patients.
compared with that in healthy controls as well as with that in moderate and severe patients (p < 0.05). Both IL-17 and IL-25 productions did not significantly differ in activated PBMCs from different severity subgroups (data not shown).

**Correlations between Th17 Cytokine Concentrations and Th1 or Th2 Cytokine Productions in Allergic Asthmatics**

To figure out the possible interactions between Th17 cytokines and Th1 or Th2 cytokines which were altered in allergic asthmatics, we further studied whether the concentrations of IL-17, IL-22 or IL-25 were correlated with those of other cytokines by Spearman nonparametric test. As shown in figure 4, IL-17 concentrations were positively correlated with IL-23 concentration both in plasma and in activated PBMCs (r = 0.526, p = 0.003 and r = 0.428, p = 0.021, respectively). We found no correlation between IL-17 concentration and other cytokine productions. The level of IL-22 or IL-25 was not correlated with that of other cytokines (data not shown).

**Expression of RORγt mRNA in PBMCs**

RORγt is the key transcription factor controlling the differentiation of Th17 cells. Enhanced numbers of Th17 cells and productions of IL-17 in allergic asthmatics may be due to the increased expression of RORγt. The level of this transcription factor in activated PBMCs was analyzed by RT-PCR. As shown in figure 5, the level of RORγt mRNA was significantly increased in activated PBMCs in allergic asthmatics compared to healthy controls (p < 0.05).

**Discussion**

In this study, we demonstrated an increase in circulating Th17 cells and more production of Th17-related cytokines in plasma and activated PBMCs in allergic asthmatics than in healthy controls, suggesting that Th17 immunity was possibly involved in the systemic immune responses of allergic asthma. Th17 is a novel CD4+ effector T cell lineage characterized by the production of some distinct cytokines, especially IL-17 and IL-22. Previous studies in mice have showed that Th17 functions locally, as well as systemically, in promoting allergic asthma [12, 13]. The major effects of Th17 immunity in asthma are mediated by Th17 cytokines such as IL-17 and IL-22. IL-17 acts on airway epithelial cells, lung fibroblasts and other types of inflammatory cells to trigger the production of pro-inflammatory cytokines, chemokines and matrix metalloproteinases, promotes the recruitments of neutrophil and macrophage, and leads to tissue inflammation. Several studies reported that IL-17 was enhanced locally in bronchial biopsies, bronchoalveolar lavage fluid and sputum samples from asthmatic patients compared with those from controls [14, 15]. As a supplement to these studies, our results demonstrated a systemic enhancement of IL-17 in plasma and activated PBMCs in allergic asthmatics. The concentration of IL-17 in plasma reflects the original condition in vivo of subjects, whereas the secretion of IL-17 in vitro from activated PBMCs represents potential IL-17-producing cells such as CD4+ T cells (an important source of IL-17), CD8+ T cells, natural killer cells and so on [16, 17]. Expression of IL-22 is also found in activated T cells, especially in CD4+ T cells,
Correlations between IL-17 concentration and other cytokine productions in plasma (a) and in culture supernatants of activated PBMCs (b) in allergic asthmatics were evaluated by Spearman's rank test. $r =$ Spearman's rank correlation. * $p < 0.05$; ** $p < 0.01$. 

Fig. 4.
Fig. 5. Expressions of RORγt mRNA in PBMCs from allergic asthmatics and healthy controls. The mRNA level was detected by RT-PCR and the ratio of RORγt/GAPDH mRNA was compared between the 2 groups. * p < 0.05 versus healthy controls.
and in activated natural killer cells at lower levels [18]. IL-22 is also described as a pro-inflammatory cytokine, and IL-22 was upregulated in autoimmune diseases, such as psoriasis, rheumatoid arthritis and inflammatory bowel disease [19–21]. Consistently, our study provided evidence that the concentrations of both IL-17 and IL-22 were higher in plasma from allergic asthmatics compared with those from healthy controls, supporting a role of Th17 immunity in system inflammation in allergic asthma. The upregulation of IL-17 in plasma in allergic asthmatics can be partially attributed to the increased frequency of circulating Th17 cells, which are the major source of IL-17 in vivo. The mechanisms of the enhanced Th17 immunity in allergic asthma are still unknown.

IL-23 plays a critical regulatory role in the differentiation and function of Th17 cells, that is, it enhances IL-17 productions and promotes Th17 cell-mediated inflammatory responses [22]. A study in mice has suggested that IL-23 produced by activated antigen-presenting cells, such as dendrite cells and macrophages, could stimulate IL-23-responsive CD4+ T cells to produce IL-17, which then recruited inflammatory cells into the lung [23]. In accordance with these studies, we observed a parallel elevation of plasma IL-17 and IL-23 concentrations in allergic asthmatics, suggesting that IL-23 and IL-17 may have a functional immunological association in the development of allergic asthma. Thus, IL-23 may function as an important regulatory cytokine which is involved in the Th17-induced system inflammation of allergic asthma.

In addition to IL-23, the differentiation and function of Th17 cells are also regulated by RORγt, an essential transcription factor involved in the generation of human Th17 [24]. Both the maintenance of cytokine production in Th17 cells in vitro and Th17 cell-mediated inflammatory diseases in vivo require the induction of RORγt [23, 24]. Here we found that allergic asthmatics had a higher expression of RORγt at mRNA level compared with healthy controls, which suggested that higher levels of Th17 cells existed in allergic asthma at least at the transcriptional level. The mechanisms that initiate the aberrant transcription of RORγt in asthmatics are still unknown.

Furthermore, we evaluated the differences of the expression of Th17 cytokines among allergic asthmatics with different severity. We found that the percentages of Th17 cells as well as the plasma concentrations of IL-17 and IL-22 were remarkably higher in severe allergic asthmatics than in mild and moderate patients, suggesting that the Th17 cells and the expression of IL-17 and IL-22 seemed to increase with the severity of allergic asthma. IL-17 can stimulate the release of neutrophil-mobilizing cytokines, which then induce airway neutrophilic inflammation, predominantly in acute, severe exacerbations of asthma or severe asthmatics [25]. Similar to our finding, a study showed that patients with severe asthma had increased neutrophils and eosinophils in sputum compared to moderate and mild asthmatics [26]. Based on these evidences, we postulate that the increased levels of Th17 cells and cytokines in severe allergic asthmatics may be associated with neutrophilic inflammation, and the plasma concentration of IL-17 or IL-22 might be an indicator for the severity of asthma. These results also suggest that Th17 immunity participates in the development of allergic asthma as an enhancer.

An unexpected finding in this study is that high levels of IL-4 and IL-17 in plasma were also found in allergic asthmatics, even though these patients were treated with inhaled glucocorticoid. This is inconsistent with a study which demonstrated that oral glucocorticoid treatment reduced the level of IL-17 in bronchial biopsy specimens [27]. This discrepancy may be due to the local effect of inhaled glucocorticoid which does not suppress the systemic Th2 and Th17 immunity. However, steroid resistance in these patients may be another important explanation. It has been reported that atopic asthma can be divided into steroid-responsive eosinophilic asthma and steroid-resistant noneosinophilic asthma. The latter is mostly severe, predominantly mediated by non-Th2 immunity and neutrophilic inflammation [28, 29]. Moreover, IL-17 has been considered to induce and mediate neutrophilic inflammation [30]. Taken together, these data suggested that inhaled glucocorticoid treatment could not suppress IL-17-driven airway neutrophilic inflammation in these patients. Additionally, this is confirmed by a study in mice which showed that dexamethasone treatment could not attenuate the neutrophil influx to the airway in Th17 cell-transferred mice after allergen challenge [31]. Therefore, Th17 immunity may provide us with a new insight into the classification of the non-Th2 immunity type of asthma.

We also observed that IL-25, another IL-17 family member, was increased in allergic asthmatics compared with that in healthy controls. Being members of the same cytokine family, IL-25 has a different function in the pathogenesis of allergic asthma. IL-25 was initially found to be secreted by activated eosinophils and basophils in humans [32]. Interestingly, these cells obtained from allergic patients produce more IL-25 than those from healthy controls after activation. It has been shown that
IL-25 could induce and amplify Th2-allergic inflammation by inducing the production of IL-4, IL-5, IL-13, IgE and eotaxin, promoting mucus secretion and airway hyperreactivity [32]. In our study, we found that the level of IL-25 was higher in mild allergic asthmatics than in other groups. This could be explained by the predominant Th2 and eosinophil-dominant inflammation in mild asthmatics. Therefore, IL-25 may be involved in the development of allergic asthma probably associated with eosinophil and Th2 response. The distinct expression patterns and biological activities of IL-17 and IL-25 implicate that they may play different roles involved in Th17 immunity in the pathogenesis of allergic asthma. And the possible mechanism may be that IL-17 acts on the innate effectors during the onset of allergic inflammation. Then, IL-25, produced by innate effectors, may maintain the capacity of IL-25R-expressing allergen-specific Th2 cells and amplify the Th2 immunity. Consequently, a positive feedback loop between innate and adaptive immunity and critical regulation of adaptive immunity lead to the development of allergic inflammation. Further experiments are needed to assess the concentrations of the 2 cytokines as well as the numbers of neutrophils and eosinophils in blood, bronchoalveolar lavage fluid and tissue, to give more information about their functions.

Finally, we also found that the proportions of Th2 cells increased and Th1 cells decreased in allergic asthmatics compared with those in healthy controls. There was no difference of Th1 cytokine secretion in plasma and activated PBMCs between the 2 groups. However, the ratio of Th1/Th2 cytokine in allergic asthmatics was lower than in healthy controls, which was in agreement with the Th1/Th2 imbalance theory and confirmed a predominance of Th2 immunity response in the pathogenesis of allergic asthma.

In conclusion, the elevated plasma IL-17 and IL-22 and circulating Th17 cells are important features of allergic asthma and the Th17-driven immunity is paralleled with the severity of asthma. Increased expression of regulatory cytokine (IL-23) and transcription factor (RORγt) may contribute to the abnormal Th17 immunity in asthma. Elevated plasma IL-25 may be associated with mild asthma. The causal role of Th17 immunity in the pathogenesis of allergic asthma needs to be further illuminated. In future studies, which should be based on a larger scale of the population, different classifications of asthma and further experiments on cellular mechanisms are required.

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