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B cells abnormalities in asthma

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Abstract. Asthma is a chronic inflammation in the respiratory tract, which is an abnormal immune response of type I allergic reaction with elevated IgE levels. The abnormality of B cell contributing to asthma development has not been elucidated completely. Recently, data from different research groups showed that both $CD27^{+}CD38^{+}$ plasmablasts and $CD24^{hi}CD38^{hi}$ transitional B cells are capable to induce the production of IgE antibody. In contrast, Bregs is crucial for inhibiting type 2 inflammation through secreting cytokines IL-10 in asthma patients of both children and adults. With the advancement of high-throughput sequencing and analysis technology in recent years, there has been further displaying of the association between B subgroups and asthma besides Breg and plasmablast subsets. This article briefly summarized the pathogenesis and pathological progression of Breg cells in animal models and patients of asthma, with a particular focus on high-throughput sequencing revealing new mechanisms and diagnostic and therapeutic targets of Breg cells in recent years, providing new evidences for the study of asthma pathogenesis and directions for the treatment of asthma.

Keywords: asthma, highthrough put sequencing, B cells, Breg.

1. Introduction

More than 300 million individuals suffered asthma globally, mainly affected children and adolescents, resulting in pressure on healthcare systems worldwide and patients' family due to declining of life quality [1]. The abnormal up-regulation of IgE levels in asthma indicates the pathogenesis of activated B cells in disease development [2]. However, the mechanisms of B cells abnormality in asthma is still unclear. Recently, the Breg subsets were focused on in allergic asthma since these cells express IL-10 cytokines with inhibition of inflammation in airway tracts through suppressing the IgE-mediated allergic responses. For instance, data from the animal models of asthma showed that some kind of parasites relived the symptoms of asthma through secreting IL-10 in Bregs, such as suppression of inflammation and hyperresponsiveness in airway. Moreover, the effects of allergen immunotherapies in asthma patients are associated with the increment of Bregs through production of IL-10, thus leading to suppression of immune overreaction to specific allergens such as cow milk and bee venom [3].

With the advancement of high-throughput sequencing and analysis technology in recent years, there has been further explaining of the role of B cells besides Breg subsets in asthma [2]. This article briefly summarized the pathogenesis and pathological progression of Breg cells in animal models and patients of asthma, with a particular focus on high-throughput sequencing revealing new mechanisms and

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diagnostic and therapeutic targets of Breg cells in recent years, providing new evidences for the study of asthma pathogenesis and directions for therapeutic asthma.

2. The pathogenesis of Breg cells in asthma

The down-regulation of Bregs in the lung of asthmatic mice exposure to allergen, suggested the abnormal functions of B cells contributing the disease progression. Recently, Qian et al. found that IL-10 declined in Bregs of asthmatic patients, further suggesting their pathological roles in asthma since they revealed that these cells declined the expression of Bcl-3. Subsequently, these authors displayed the roles of these Breg subsets in asthmatic mice, showed that the infiltration of eosinophils in airway, the proliferation of airway goblet cells, the hyperresponsiveness of airway, and the secretion of epithelial chemokines were significantly increased in the lungs of HDM-induced asthma in comparison with control groups. These data suggested that the Bcl-3 possible inhibited the functions of Bregs in asthma, thereby inducing the pathological progress of asthmatic mice, thus targeting the signal axis possibly become an optimistic candidate in treatment for allergic asthma [4].

In addition, similar to the results of mice models, researchers' data showed that the numbers or percent of some Breg subsets with special markers declined in asthma patients. For instance, the circulating Breg subsets with high expression of CD24 decreased in both proportion and numbers in patients with allergic asthma, which expressed low level of IL-10 even using LPS stimulation. Moreover, frequencies of Bregs with high expression of CD5 are also decreased in adult allergic asthmatics. Recent research data revealed that $CD24^{+}CD38^{+}$ Bregs in circulation have significantly decline in pediatric asthma patients accompany with low expression of IL-10 in comparison with the healthy controls. These results demonstrate that execrated inflammation leads to the development of asthma, eventually increased the morbidity of patients [3]. Therefore, Bregs play crucial roles in the pathogenesis of allergic asthma including secreting cytokines to inhibit Th2 inflammation.

3. Recent advances in Bregs abnormalities and asthma

3.1. B cell mediated pathogenesis in asthma

The chemokine of CXCL13, as a cytokine of B-cell activation, induced the progression of asthma through recruitment B cells to bind its receptor of CXCR5. The data of Alturaiki showed that both CXCL13 and its receptor were increased significantly in asthma compared to controls. In addition, the levels of them were positive correlation with the severity of asthma, suggesting this signal axis involved in asthmatic inflammation [5]. Another cytokine, BAFF is capable to induce activation of B cell, contributing to the development of allergic asthmatic inflammation through inhibition cytokines of Treg cells, such as IL-2 and TGF-β. Therefore, suppression of BAFF decreased airway inflammation, thereby protecting from asthma in transgenic mice through reducing infiltration of inflammatory cells in the airways, especially eosinophils. Similar to the results of BAFF-transgenic asthmatic mice model, the airway inflammation is relative severe compared to control animals in APRIL-deficient mice. Similarly, other studies, using a TACI-Ig decoy receptor recognized BAFF or APRIL inhibited Th2 cells mediated airway inflammation and asthmatic symptoms using transgenic mice [6].

Subsequently, researchers further explored the influence of B cells on asthma using wild-type and genetic mice, such as B-cell or IL-10 deficient mice and IL-10-transgenic mice. In comparison with wide-type mice, genetic mice are susceptible developed AHR with more server damage in measurement of lung functions *in vivo* and pathological staining *in vitro*. Moreover, pathological staining showed that the deposition of collagen was significantly increased in genetic mice of allergic asthma, demonstrating more serious airway remodeling, which were negative relation with the number of regulatory T cells. Interestingly, adoptive transfer of B cells over-expression IL-10 attenuated remodeling and AHR in asthmatic lung of mice, as well as the increasing number of FoxP3+ regulatory T cells, suggesting an optimistic candidate using B-cell-targeted strategies in the treatment of asthma [7].

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Recently, Tan's group focused on other B cells subsets including immature B-cell populations and memory B-cells. Their data showed that the imbalance of these two B subgroups were obvious in severe asthmatic patients compared to healthy controls with up-regulation of immature B and down-regulation of memory B cells. The authors further detected the proportion of IgA^+ memory B-cells and analysed the correlation between this subpopulations and the dysfunctions in small airway and infection frequency in respiratory tracts. The level of CD27 expression in this subgroups correlated with the numbers of sputum eosinophils using flow cytometry and pathological staining. Equally, the patients with higher $CD27^+IgA^+$ B cells more severe declined in lung function and life quality after assessment using ACQ-7 questionnaire [8].

Further analyzed B cells in sputum revealed the secreted level of IgG and IgA in $CD27^-IgD^-$ transitional B cell such as auto-antibodies for EPX. Correlation analysis of this kind of B subgroups in sputum and its secretion of auto-antibodies with clinic symptoms showed positive significant correlation, demonstrating this B subpopulations involved in the pathogenesis of asthma through autoimmune reactions in airway [8].

3.2. Targeted B cells to diagnose, monitor, and treat asthma

From the above part summary, B cell activation associated factors, such as BAFF and its receptor, APRIL, TACI and BCMA, contribute to the pathogenesis in asthma. Alturaiki's group detected the concentration of BAFF and APRIL and their receptors, then analyzed the correlation between the level of these cytokines and the production of IgE using 47 patients and 20 healthy controls. The results showed that these cytokines and their antibodies and IgE antibodies markedly increased in patients with asthma compared with healthy controls, implicating that these factors possible a prospective monitoring method for symptoms and treatment response in asthma [6].

As the above described, IL-10 has key roles in inhibition of immune responses through suppression activation and proliferation of related immune cells and epithelial cells. In contrary, the Bcl-3 knockout mice showed elevated IL-10 levels, leading to server allergic asthma in HDMs models through upregulation of CCL-20 in both dendrtic cells and lung epithelial cells. Interestingly, blockade IL-10 signal pathway using recombinant proteins or antibodies suppressed both sensitization and asthma development through regulation Bcl-3 signaling axis. Therefore, the inhibition of allergic sensitization using genetic mice implicated targeting this signal pathway is a promising approach for treating allergic asthma [4].

3.3. Data from high throughput sequencing

The Breg cells are capable of suppressing allergic responses through inhibiting FoxO1 expression , thus inducing IL-10 secreting. Consistent with the previous data, Wang's group also showed that knockout of FoxO1 increased the proliferation of B10 cells. Further, this group also found knock out the gene of FoxO1 in B cells decreased infiltration of eosinophils in lung tissue in asthmatic mice through suppression of the Breg's number. The correlation analysis showed that the expression of FoxO1 was negative correlated with the level of IL-10 in B cells in the tissues of patients and models using sc-RNA sequencing technology, such as lung and spleen. Further, they also studied the treat mechanisms of Bregs was that FoxO1 negatively regulated the expression of Prdm1, inhibiting protein level of Blimp-1, thereby contributed to allergic asthma in both mice model and human patients [9].

In a recent study, researchers identified four genes related to the IgE secretion using TWAS technology. The gene of *CLC* is associated with the infiltration of eosinophils and secretion of IgE, which has been known. The genes of CCDC21 and S100A13 are novel findings in the present study with little known about the relationship to the level of eosinophils and IgE. In addition , the author found the gene of *GCNT1* was an optimistic candidate as for drug target since it regulated immune reaction besides relationship with IgE level in allergic asthma patients [10]. The mechanisms of Bregs cells in asthma and related targeting treatment are list in Table 1.

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Table 1. Bregs in asthma.

Classifications	Examples
Pathogenesis	The $CD24^{+}CD38^{+}$ and $CD5^{+}$ Bregs in circulation have significantly decline in pediatric asthma patients [3]. The IL-10-producing Bregs were inhibited by the expression of Bcl-3 in allergic asthma [4]. The TACI-Ig decoy receptor recognized BAFF or APRIL inhibited Th2 cells mediated airway inflammation [6]. FoxO1 contributed to allergic asthma through negatively regulation Blimp-1 in Bregs [9].
Treatment	Targeting the Bcl-3/IL-10 axis may be a optimistic candidates in treatment for allergic asthma [4]. The adoptive transfer of IL-10-proficient B cells attenuated AHR and lung remodeling in HDM-mediated asthma [7]. The gene *GCNT1* was an optimistic candidate as for drug target in allergic asthma [10].

4. Conclusion

The abnormality in B cell-mediated humoral immunity with high level IgE involved asthma development. Recently, data from different research groups showed that plasmablasts with high expression of CD24 or CD27 or other transitional B cells contributed to IgE antibody production. In addition, the number and function of Bregs are important for both children and adults with allergic asthma due to their releasing IL-10 cytokines to inhibit airway inflammation. Recently, high throughput sequencing technology displayed some novel genes associated with the IgE level in asthma patients. The advancement of high-throughput sequencing and analysis technology will understand deeply the impact of genomic variants, cellular heterogeneity and protein-protein interaction network in the pathogenesis of asthma, thus promoting the novel drugs transforming to clinic application in time.

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