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Discovering Biomarkers of Neutrophilic Asthma: A Researcher's Perspective

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Abstract

Asthma is a chronic inflammatory disease of the airways characterized by inflammatory responses, airway hyperresponsiveness, reversible airway obstruction, and airway structural remodeling. It is a key therapeutic target for this inflammatory pathway, although neutrophilic airway inflammation occurs most often in steroid-insensitive asthma, severe asthma, asthma exacerbation, and occupational asthma. We currently lack biomarkers for the diagnosis of neutrophilic asthma. In this issue of allergy, asthma and immunology research, Bich et al. analyzed adult asthmatic patients and healthy control subjects, and found significant differences in serum SAA1 levels. From the perspective of basic research, our team puts forward some views and opinions on the problems and short comings of this research, and expects more researchers to pay attention to the research of asthma. We believe that the interrelationship between IL-6 and SAA1 in asthma is worth exploring despite some imprecisions in this study.

Keywords: Neutrophilic asthma; SAA1; Biomarkers; IL-6

Subject

Asthma is a chronic inflammatory disease of the airways characterized by inflammatory responses, airway hyperresponsiveness, reversible airway obstruction, and airway structural remodeling [1]. A large number of studies have shown that airway inflammation is the main factor in the pathogenesis of asthma, and a large number of cytokines, chemokines and other pro-inflammatory mediators released by inflammatory cells and airway intrinsic constituent cells affect the occurrence and development of asthma and the regression of the disease [2]. Asthma has long been associated with eosinophilic inflammation and IgE-mediated mast cell activation, and suppression of airway inflammation by inhaled corticosteroids has been a routine approach in asthma treatment [3]. However, neutrophil infiltration is also observed during asthma exacerbations, and more neutrophil infiltration is usually observed in patients with severe asthma who are refractory to steroids. The role of neutrophils in the pathogenesis of bronchial asthma is controversial [4]. Main stream studies suggest that type 2 helper lymphocytes, innate lymphocyte populations and related cytokines play a key role in asthma, and eosinophils are the mediators of this disease [5]. It is a key therapeutic target for this inflammatory pathway, although neutrophilic airway inflammation occurs most often in steroid-insensitive asthma, severe asthma, asthma exacerbation, and occupational asthma.

We currently lack biomarkers for the diagnosis of neutrophilic asthma. Some researchers define eosinophilic asthma as more than 3% eosinophils in sputum and neutrophilic asthma as more than 76% neutrophils in sputum, apparently by looking at the proportion of cells in sputum to determine the type of asthma [6]. The distinction can easily lead to misdiagnosis. Biomarkers are measurable indicators that reflect the presence and severity of the disease or evaluate the effect of treatment, and are an objective and measurable way to represent the course of the disease. In this issue of allergy, asthma and immunology research, Bich et al. [7] analyzed adult asthmatic patients (n=122) and healthy control subjects (n=60), and found significant differences in serum SAA1 levels between the two groups, NA group (n=78) was also significantly higher than the Non-NA (n=44) group. When SAA1 was determined as a threshold level of 2.6 ng/mL, asthmatic patients with high serum SAA1 levels had significantly lower forced expiratory volume in 1 second (81.4 ± 20.5% *vs.* 89.4 ± 14.3%; P=0.018), sputum neutrophils Cell counts were higher (77.3 ± 28.0% *vs.* 61.8 ± 34.7%; P=0.031), and the authors suggest that SAA1 is potentially associated with neutrophilic asthma. The authors then used two types of epithelial cells to demonstrate that SAA1 may be derived from epithelial cells and briefly observed the effect of SAA1 on neutrophil and macrophage function. Using an animal

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model of asthma, it was observed that the NA group had higher levels of SAA1 and significantly increased the number of CD4+ T cells. This work not only proposes that SAA1 may be a potential biomarker for neutrophilic asthma, but also briefly explores the mechanism by which SAA1 affects the immune system. In this editorial, however, I want to assess the findings and ask questions as a researcher and with my current understanding of the research work. First, SAA1 is generally thought to be an acute phase response protein secreted by the liver, which is multiplied at the onset of disease [8]. After reviewing the literature, it was found that the general SAA1 serum content is ug/mL as the result reporting unit, which is 3 orders of magnitude different from the results reported in the paper [9]. There are many factors affecting the determination of FEV1%. Many indicators including FEV1% in the HCs group were not detected. In addition, the article simply mentioned the use of the Global Initiative for Asthma (GINA) 2020 guideline as the diagnostic standard. Disease will raise SAA1 does not strictly propose the exclusion criteria of the population. Combining the above two reasons, it is difficult to objectively agree that SAA1 in peripheral serum is significantly increased in asthmatic patients. The results of the FEV1% value of the High-SAA1 group was significantly lower than that of the Low-SAA1 group, but FEV1% was not the gold standard for diagnosing asthma, nor could it distinguish the pathological types of asthma. The Sputum neutrophil counts of some patients in the Low-SAA1 group were also greater than 65% (the standard for diagnosing NA), and the SAA1 serum level was not correlated with the percentage of neutrophils in the sputum. Molecular hallmarks of granulosa-type asthma. Second, the asthma model is questionable. The article uses OVA as the model drug, Poly I-C as the sensitizer, and different concentrations of LPS as the drug to induce the three models of EA, NA, and MA. OVA, also known as ovalbumin, easily induce an allergic reaction in BABL/c mice that produces airway hyper responsiveness and IgE hypersensitivity in serum, and is often used to construct an allergic mouse asthma model [10]. Some researchers have used respiratory syncytial virus to stimulate asthma in mice instead of using Poly I-C, so the use of OVA instead of virus in animal models is not convincing enough [11]. LPS is a component of the outer wall of Gram-negative bacterial cell walls. LPS stimulates a strong systemic inflammatory response in the host, including cellular and humoral responses mediated by Toll-Like Receptor 4 (TLR4), which can activate almost all immune cells [12]. There is no evidence that certain types of immune cells are activated only by specific concentrations of LPS, so the three models of EA, NA, and MA are also questionable. Third, macrophages are the most abundant immune cells in the lung, have strong plasticity, and can show different activation states due to changes in the tissue microenvironment, which can be divided into classical activation M1 and alternately activated M2 [13]. M1 macrophages are typically polarized by Th1-related cytokines such as Interferon Gamma (IFN-γ) and microbial stimuli such as Lipopolysaccharide (LPS) recognition, while M2 macrophages respond to Th2 cytokines. Increased polarization and activation of M2 macrophages has been observed in asthma, which has been suggested to play an important role in allergic asthma [14]. In the article, only one factor of iNOS is detected to observe the polarization phenotype of macrophages, which is slightly incomplete. It would be more convincing if several indicators were detected, especially the markers of M2 cells were detected at the same time and the same conclusion could be obtained. The article mentioned whether there is a scientific basis for monocytes cultured for 7 days to become M0 macrophages. The current routine practice is to use PMA to stimulate monocytes to change from suspension to adherent state, and then M0 macrophages are considered [15]. Induction success. In addition, the article mentioned that the SAA1 serum concentration of 2.6 ng/mL is a cut-off point. The data that the maximum serum content of patients is about 2.9 ng/mL. It is reasonable to use a high concentration of 50 ng/mL to act on cells and then detect molecular markers. The results of the WB experiment simply observed that the difference in iNOS was not so significant with the naked eye, so whether the difference was related to the inconsistency of the cell plating density, the results are the number of cells in each group was significantly different. Finally, we found an interesting problem. Interleukin 6 (IL6) is a pleiotropic cytokine with pro- or anti-inflammatory effects, depending on the cellular environment and pathophysiological state. The results are the serum IL6 content of patients in the high SAA1 group was higher than that in the low SAA1 group. The results that are epithelial cells stimulated by IL6 can significantly increase SAA1 content (although intracellular and culture medium were not tested in the article), on the contrary, SAECs stimulated by SAA1 can significantly increase IL6 content. SAA1 at 50 ng/mL increases the production of so-called IL6 in macrophages, and the lack of SAA1 in the 2.6 ng/mL dose group is what we do not know about IL6 production at this time. Studies have found that IL6 inflammation is closely related to asthma and is positively related to disease severity [16]. Cellular IL6 levels are generally low under physiological conditions, and although many stimuli lead to induction of IL6 expression and secretion, especially during the acute inflammatory response to infection, cellular production of IL6 is critical for the induction of acute-phase proteins, but the Overproduction drives chronic inflammation, and elevated systemic levels of IL6 have been linked to conditions such as autoimmune disease, arthritis, hepatitis, inflammatory bowel disease pancreatitis, and cancer. Or IL6 may be a key target for the treatment of asthma. Although there are certain problems, the work of Bich et al. has brought a lot of ideas and references to the search for neutrophilic asthma. If you can use knockout mice for experiments or try SAA1 antibodies for neutrophilic asthma treatment, it may bring more surprises.

In conclusion, in-depth research on the pathological mechanism of neutrophilic asthma and the discovery of new therapeutic targets and diagnostic molecular markers are of great significance for the precise treatment of the disease.

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