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Asthma immunopathogenesis and biomarkers in asthma treatment

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Abstract

Asthma is a disease that affects millions of people all over the world. In terms of socio-economic status, especially low and medium-level countries are more affected by this situation. Intestinal and lung microbiota play an important role in the basis of the disease. In previous years, the paradigm between Th1 and Th2 was thought to be responsible for airway inflammation in asthma. But over the years, Treg and Th17 cells, which are subgroups of these cells, have been discovered, unlike Th1 and Th2 cells. It was thought that the connection between these cells may also be an effective factor in asthma. In the following years, it was possible to gain knowledge by using factors such as onset of symptoms, presentation of symptoms, allergy, eosinophil and disease severity in determining phenotypes. Today's biotechnological developments are increasing rapidly. In this way, there are developments in the field of targeted therapy.

Introduction

Asthma is a disease that affects children and adults of different age ranges. Airway remodeling, reversible airway obstruction, excessive mucus secretion, airway hyperresponsiveness, and chronic airway inflammation in the form of recurrent attacks, which are characteristic features of asthma [1]. The frequency of the disease varies between populations, but it is one of the most common respiratory diseases affecting children and adults [2]. The disorder affects 300 million people around the world. In our country, this situation is approximately 3.5 million [1]. The characteristics of this disease is shortness of breath, wheeze, cough and a feeling of pressure in the chest. These symptoms are evident in the morning or at night, recurring at regular intervals, occur or worsen after exposure to irritants (infection, cigarette smoke, exercise, cold air) or allergens (cat hair, pollen, house dust mite, etc.) and recovery on its own or with appropriate treatment is the classic symptom pattern [3].

Environmental and genetic factors, which are the main causes of asthma, cause this disease to be heterogeneous [4]. In addition to these, there are also epigenetic and etiological factors. Atopic, one of the etiological factors, constitutes 50% of asthmatic patients. However, asthma development is observed in a small number of atopic patients. The conclusion to be drawn from here is that asthma is an unpredictable disease [5]. Human genetics contributes to the pathogenesis of asthma [4]. Many genes are involved in the pathogenesis, and over 600 genes have been identified that are associated with asthma. Despite this high number, only a few of these genes have been replicated. Asthma-associated signaling proteins include beta 2 adrenergic receptor gene, cytokines, receptor genes of transcriptiom factors involved in Th1 and Th2 cell differentiation. STAT6, GATA3, IL-4, IL4RA, ADAM, TBX21, IFNG, IFNGR1, TLR4, FCER1B, CD14, IL13 and IL13 receptors are among the genes associated with asthma. In addition to beta-2 agonists, genes responsible for regulation of the response to leukotriene antagonists and steroids have also been identified in asthma. We can collect the genetic changes associated with these genes under four main headings:

a- Production of antibodies in the IgE structure specific to the allergen (atopy),

b- Genes that have an effect on the hyperresponsiveness of the airway,
c- Inflammatory mediators whose synthesis is affected by some genes (growth factors, cytokines and chemokines),
d- Th1 in relation to the hygiene hypothesis and determining the balance between the Th2 immune response [6].

In airway inflammation associated with asthma, basophils are associated with infiltration of cells such as T helper (Th) cells, eosinophils, and mast cells in the airway submucosa. Airway epithelial cells form the first line of defense against respiratory environmental factors such as pollutants and pathogens. One of its functions is to initiate airway inflammation. As a result of the initiation of inflammation, different cell structures are stimulated and the release of interleukin-25 (IL-25), IL-4, IL-9, IL-13, IL-5, IL-33, thymic stromal lymphopoietin (TSLP) cytokines is initiated. As a result, IgE synthesis takes place. The allergen-specific IgE receptor, which is carried by mast cells, starts airway inflammation by causing leukotriene, prostaglandingin and histamine release as a result of re-exposure to the antigen. Within the allergic and non-allergic phenotypes of asthma, a number of changes occur in the dynamic structure that includes all layers of the bronchial wall of the small and large airways. With the inclusion of biological mechanisms, the resulting changes initiate the "remodeling" transformation, which is determined by the increase of bronchial vasculature, thickening of smooth muscle cells, subepithelial thickening, and epithelial changes [7]. With high-dose allergen intake, there is a shift from allergic Th2 inflammation to Th1 inflammation and the formation of regulatory "suppressor" lymphocytes called Treg (T regulator) [8]. Treg cells are the cells whose basic function causes suppression of the immune response in periods when it is not needed. This mechanism is mainly useful in eliminating the pathogenic microorganism as a result of infection and suppressing the autoimmune response. Th2-related inflammation can be exploited to control the increased function of Treg cells in asthma [9]. Mild to moderate allergic asthma is characterized by Th2 cell-mediated hyperplasia of mucus-secreting cells, eosinophil infiltration, remodeling, bronchial hyperreactivity and metaplasia. In severe asthma, neutrophil inflammation and infiltration induced by INFγ, TNFα, IL-25 and IL17 cytokine variants are thought to be responsible for the development of resistance to corticosteroids [5]. As a result of the comparison of asthma patients with healthy individuals, an increase in IL-17A+ cells was observed in peripheral blood mononuclear cells. In addition, IL-17A mRNA was found to be responsible for increasing inflammatory mediator synthesis in fibroblasts isolated from bronchial biopsy in asthma patients [9]. The orientation of the treatment of asthma to targeted therapy has been with the discovery of omalizumab and, more recently, anti-cytokine and anti-cytokine receptor antibodies. To date, physicians have gained knowledge of asthma phenotypes based on the onset of symptoms, allergies, eosinophils, presentation of symptoms, and severity of the disease. The mainstay of asthma treatment is inhaled corticosteroid (ICS) therapy. The reason is that the basis of asthma is accepted as eosinophilic inflammatory.

Until recently, traditional treatment was always used due to the lack of biomarkers used to identify different types of asthma. Today, there are different treatment methods for homogeneous groups, thanks to endotype and phenotype classifications according to biomarkers and physiological-clinical characters. While the concept of endotype deals with the occurrence and molecular mechanism of the disease, the concept of phenotype is the clinically observed features. They define the pattern and determine the physiological and clinical characters. Understanding whether patients respond or not to treatment is thanks to the use of biologic agents in phase studies and in the clinic. Owing to the observed heterogeneity, asthma has been further subdivided into specific subgroups.

In the coming years, it is possible to perform a more detailed analysis of gene expression in patients who have responded to treatment. This analysis will enable the further development of further analysis and to identify specific biomarkers for treatment targets. The reason why the concept of personalized medicine is acceptable is that it leads to an endotype definition for each patient that addresses the causal pathways. The main rationale in personalized treatment is to ensure that phenotyping is done in an unbiased manner. In the definition of a biomarker, it is expressed as that which can be measured and evaluated as an indicator of normal or pathological biological processes or a biological response to a therapeutic challenge. Defining biomarkers as predictive markers and increasing our capacity of the response allows us to make reliable and accurate determinations. In the treatment of asthma, mostly a Th2 biomarker is utilized for the diagnosis of the disease. These biomarker types also include serum IgE, exhaled exhaled nitric oxide level, blood eosinophil count, sputum eosinophil count, and serum periostin levels. Today, biomarkers are used more and more to identify patients specifically [10].

Results

Gender, body mass index and age are important factors in the phenotyping of patients with asthma. The reason for this is that asthma at an early age is related to the atopic phenotype. In addition, the patient should be questioned more in situations such as exercise that trigger asthma symptoms. Determining the number of exacerbations per year is an important factor in defining poor asthma control. This factor is an important variable to classify as a frequent exacerbation group and also to advance the patient one step in the treatment. Two of the

most important features of biomarkers in asthmatic patients are that they enable the identification of all phenotypes covering the asthma range and identify patients who can respond specifically to treatments [8].

Conclusion

In order for biomarkers to benefit clinicians, the identification of asthma molecular phenotypes, especially non-Th2 pathways, is an important element in the coming years. For these definitions, predictive biomarker and more phenotypes should be developed. Because in the goal of targeted therapy, there is a need for a biomarker capable of predicting the response. A point to be considered in defining the phenotype is to define the asthma phenotype in an unbiased manner. While creating the patient's phenotype, the final goal of the applicability of personalized medicine, it is important to have sufficient information about the patient's environment and condition [8].

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