Immunomodulation as the desired therapy in some cases of allergic diseases

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ABSTRACT

There has been a strong belief for many years that there is no pathogenic connection between allergy and autoimmunity. Academic books usually describe the disparate immune mechanisms playing pivotal role in pathogenesis of allergic and autoimmune diseases. A simplified hypothesis of Th1/Th2 balance disorder represents an accepted model of the diseases. Recent findings have suggested that there is no clear dichotomy between allergy and autoimmunity. Both of them result from dysregulation of the immune system. The systematic review of the literature was performed searching electronic databases for the pathologic and clinical intersection of allergic and autoimmune conditions. Research is currently focused on the key elements that regulate the immune response. Mast cells, which play important role in allergic inflammation, may make it likely that they have profound effects on numerous autoimmune conditions. Environmental stress and proinflammatory cytokines may activate the protein kinases in both conditions. The presence of autoantibodies in some allergic conditions such as asthma or atopic dermatitis may point out an autoimmune background in some cases. Genetic factors lead the development of autoimmunity and allergy. The infection also may play an important role in the induction of the diseases. Despite the use of more effective anti-inflammatory drugs, the progression of many allergic and autoimmune diseases may not be halted. Better knowledge about the considerable communication between complex signalling pathways point out immunomodulation as the key to successful therapy of both allergic and autoimmune conditions.

INTRODUCTION

Allergic diseases are very common and represent a major health problem worldwide. There has been observed an epidemic increase in prevalence of allergy in the last decades in many countries. It is estimated that 10 – 30% of the population is affected.1,2. Because of their chronic, incurable, and sometimes life-threatening course, these diseases may be a significant socioeconomic burden. In many cases the diagnosis and treatment of affected individuals is insufficient and/or inadequate. In spite of great progress in research into the pathogenesis and treatment of allergy in the last few decades, there are still many problems to be resolved. Allergic diseases show a wide heterogeneity involving different organs such eyes, skin, respiratory and digestive tract. Allergic problems present variability in severity and clinical course which are at the present time only poorly defined. More precise definition of the clinical subtypes (phenotypes) of allergic patients appears important and necessary to address the right therapy to the right patient.3 Some authors of academic books underline clear border between allergy and autoimmunity. The typical pathologic pictures would not suggest a similarity in pathogenesis of allergic and autoimmune disorders. Most cases of rhino-conjunctivitis or asthma are characterised by activity of Th2 (T-helper type 2) lymphocytes and Th2-derived cytokines as interleukins: IL-4, IL-5, IL-13 and stimulation of eosinophil-predominant inflammation. On the contrary putative autoimmune disorders such as rheumatoid arthritis or type 1 of diabetes mellitus are thought to be mediated by Th1 (T-helper type 1) lymphocytes and Th1-derived cytokines as interleukins: IL-2, IFNγ. The most popular simplified hypothesis of Th1/Th2 imbalance attempts to explain ethiopathology of certain diseases.4,5. However, in recent years, findings of some studies have suggested that there is no clear dichotomy between allergy and autoimmunity. Both of them result from dysregulation of the immune system. In recent years interest of investigators is focused on the key elements that regulate the immune response in many allergic and autoimmune diseases: mast cells, autoantibodies, T-cells, cytokines and genetic determinants.6,7,8,9,10. It is obvious that mast cells play important role in allergic inflammation. But they may have also profound effects on numerous autoimmune conditions. Another factors such as environmental stress and proinflammatory cytokines may activate the protein kinases in both allergic and autoimmune diseases. There are studies in which autoantibodies have been found in some allergic conditions such as asthma or atopic dermatitis and they may point out an autoimmune background in some cases. Some recent discoveries have provided additional insight into roles of Th17 cells and T regulatory cells.11,12,13. It is obvious that genetic factors play an important role in the development and process of immunologic diseases. The studies from recent years suggest a close relation between gene polymorphism of HLA and cytokines and development of autoimmunity and allergy. The gene polymorphisms may act as risk or as protective factors12,14,15. The role of the infection also may be important in the induction of allergy and autoimmunity16,17,18. In some cases similar clinical manifestations of both immunopathologies are observed and may result sometimes in diagnostic problems. Ever-expanding knowledge about the considerable communication between complex signalling pathways point out immunomodulation as the key to successful therapy of both allergic and autoimmune conditions17. It also helps to identify promising areas for future research.

RELATIONSHIPS BETWEEN AUTOIMMUNITY AND MAST CELL-RELATED DISEASES

Epidemiological data

Epidemiological data on the coexistence of both types of mentioned disorders are scarce. Studies of the possible association between allergy and autoimmunity at the population level have come to varying conclusions. For
example in the last few decades, a positive correlation between the prevalence of asthma and the incidence of type-1 diabetes has been found at the population level, but not in the individual. Cells of these immune-mediated disorders are positively associated with the gross national product 1. In another study, Tirosch et al. analyzed data from nearly 3 years of follow up of about 450,000 population of Israeli soldiers aged from 18 to 21 years. Studies have shown an inverse correlation between asthma and BHR in patients suffering from autoimmune diseases. Autoimmune diseases are often related to the inflammatory bowel diseases, vasculitis, arthritis, and autoimmune thrombocytopenia occurred more frequently in women who have not suffered from asthma, while type-1 diabetes in men without a history of asthma 11. According to some experts opinions, extrapolating the results of this study to the general population can lead to erroneous conclusions 1. In the Medline database one can find a few publications that prove a lower incidence of autoimmune diseases in patients with allergy or atopy, or indicate a negligible difference in the appearance of autoimmune disorders in patients with previously diagnosed allergic disease in control subjects 12. Conversely, there are also reports arguing that there may be a significant percent of asthmatic women had in their clinical course. Both processes allergy and autoimmunity may show some similarities in their clinical course. Both cell related conditions and autoimmune syndromes are inflammatory processes caused by dysregulated immune response. Both disorders are complex and result from the interaction between several factors: environmental, genetic and individual. But the immune mechanisms involve similar types of cells, cytokines, antibodies, and mediators 13,14,15,16. Recent studies have also shown a close proximity of the certain genes regulating the occurrence and course of two types of diseases 15.

Pathophysiological background

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Mast cell is associated mainly with the early phase of the allergic reaction. Antigens interact with the specific IgE molecules already bound to high affinity Fc receptors on the surface of mast cells to induce degranulation. The mast cell releases a mixture of compounds, including histamine, heparin, chymase, tryptase from its cytoplasmic granules. Releasing of mediators determines the course of the early phase of an allergic reaction. But contact with the allergen also provides for the production of a number of mediators and cytokines (prostaglandins, leukotrienes, TNF-a), which will be gradually released and determine the development of the so-called late phase of allergic inflammation, which is very complicated and dependent on the number of 

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Regulatory T cells - Treg - (CD4+ CD25 + FoxP3+) appear to be responsible for the homeostasis of immune system in the healthy subjects. It is a heterogeneous group of cells that control immune response. Treg cell function might control Th2 mediated inflammation. Downregulation of these cells receptors, cytokines and mediators. The role of mast cells in the pathogenesis of allergic diseases has been well established 2,3. However, recent studies have shown the possible involvement of mast cells in the development of type-1 diabetes in children with allergic diseases, vasculitis, arthritis, and autoimmune disorders. Autoimmune diseases are complex and result from the interaction between several factors: environmental, genetic and individual. But the immune mechanisms involve similar types of cells, cytokines, antibodies, and mediators 13,14,15,16. Recent studies have also shown a close proximity of the certain genes regulating the occurrence and course of two types of diseases 15.

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The presence of increased levels of autoantibodies, sometimes specific for a single tissue, is perceived as a hallmark of autoimmunity. However, several reports suggest a possible role for autoantibodies in allergic diseases. Some patients with asthma, allergic rhinitis or atopic dermatitis have impaired sensitivity to β-adrenergic receptors. Autoantibodies directed toward the β-adrenergic receptor were found in the serum of some patients with asthma. These antibodies can block the biologic function of the β-adrenergic receptor in vitro. Previous studies have shown that the levels of IgG autoantibodies to cytookeratin 18, a bronchial epithelial cell antigen, were significantly higher in patients with asthma compared with healthy controls. Also, IgG autoantibodies and T-cell reactivity against a common SS-Kd antigen shared by platelets and endothelial cells have been found in group of asthmatics. These autoantibodies were mainly restricted to individuals with more severe, glucocorticoids-dependent, non-allergic asthma. Nahm et al reported antibody reactivity against enzyme a-enolase, which is component of bronchial cells. The presence of serum anti-enolase autoantibodies significantly distinguished patients with severe course of the disease and aspirin-induced asthma. Szczeklik et al. found the incidence of antinuclear antibodies in 55% of patients on aspirin-induced asthma, 39% of patients with allergic asthma, 41% of patients with non-allergic asthma in contrast to 11% of the control group. There is theory that antinuclear antibodies do not have a direct role in asthma pathogenesis, but indicate a susceptibility only towards autoimmunity processes due to dysregulation of immune system. For example, via reducing efficiency of Treg cells, which usually inhibits immune response against autoantibodies. The presence of autoantibodies to β-adrenergic receptors and bronchial epithelium in patients with asthma may demonstrate autoimmune phenomena in allergic conditions, although a causal link between allergy and autoimmunity has not yet been established. It means that a mechanistic link between these antibodies and an allergic condition is yet to be proven.

The role of IgE antibodies in the allergic process is obvious. Some investigation showed that the presence of IgE antibodies, however, is not exclusive to atopic disease. Specific IgE antibodies have been observed in autoimmune: anti-cyclic citrullinated peptides in rheumatoid arthritis, anti-GAD65 antibodies in type 1 diabetes, anti-TSH receptor antibodies in Grave’s disease, and anti-myelin peptides in multiple sclerosis, although the direct pathogenic role is largely unknown.

The genetic background of allergic and autoimmune disorders is represented by a complex network of interacting genes. Genome-wide studies of asthma have identified a several main regions of genome where genetic variants or disease-causing mutations are placed. Moreover, genome-wide screen in families with rheumatoid arthritis has similarly shown linkage near the asthma locus on chromosome 2 and the TCR-α locus on chromosome 14. Some findings suggest that important genes or gene families may be common to several inflammatory and immune disorders. The genes are responsible for the production of specific cytokines and mediators which determines the directions of immune response. Previous studies point out toward the transcription factors such as STAT1, STAT4, GATA3, which expression is associated with production of specific cytokines. While STAT1, and STAT4, ultimately lead to release of interferon gamma (IFN-γ), transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, and other cytokines of TH1 response, the transcription factor GATA3 is expressed and promotes further expression of IL-4, IL-5, and IL-10, and B cell-mediated humoral immunity. GATA3 activation also serves to repress IFN-γ secretion. Recent report published in Nature in 2013 indicated possible polymorphisms in a single gene of transcription factor BACH2. Genetic polymorphisms within a single locus encoding the transcription factor BACH2 may be associated with numerous autoimmunity and allergic diseases. Assessment of the genome-wide function of BACH2, revealed that it represses genes associated with differentiation of effector cell. These findings identify BACH2 as a key regulator of CD4 T-cell differentiation that prevents inflammatory disease by controlling the balance between tolerance and immunity. BACH2 is expressed in B cells. Thus, at both cellu-
Allergic inflammation as a target to immunomodulation

Despite remarkable advances in diagnosis and use of potent anti-inflammatory drugs, asthma and many other allergic diseases are still incurable. It seems that progression of airway inflammation may not be halted. Understanding of the complex pathological features of allergic inflammation may not be halted. Understanding of the mechanism of allergic inflammation is still unknown. It seems that progression of airway inflammation is still incurable. Understanding of the mechanism of allergic inflammation is still unknown.

The expression and function of these adhesion molecules and the subsequent chemotactic attraction and activation of infiltrating pro-inflammatory cells are controlled by a numerous of cytokines, chemokines, and mediators. Moreover structural cells may play important roles in the inflammatory processes. These inflammatory processes are coordinated by a complex cytokine network 1-3,6,12. Depending on the inflammatory context, cytokines often exert opposing actions and they often exhibit redundancy in their functions. Modulating the cytokine network in allergic diseases sometimes with severe course, such as asthma or atopic dermatitis with biological therapy presents a new but challenging paradigm for treatment of these disorders. The basis for immunomodulation therapy of allergic diseases was initiated by the development of Th2 predominant response. It is associated with unique cytokine profile: IL-4, IL-5, IL-9, IL-13, IL-25 and IL-33. Therapy based on this hypothesis concentrates on changing the balance of the immune system towards Th1 response. This can be done in two ways: blocking Th2 derived cytokines with antagonists (monoclonal antibodies, soluble receptors) or by stimulating Th1 response, boosting by addition of recombinant cytokines for example 11,12. Some studies showed that IFN-α-g had potential local and systemic effects on the airway epithelium. This cytokine plays role in activation of antigen-presenting cells, IL-12 production and differentiation of naive T lymphocytes into Th1 11,12. IL-12 was considered as the additional target of immunomodulation, because mouse studies revealed that administration of this cytokine suppresses antigen-induced tissue eosinophilia and inhibits IgE production. Unfortunately due to significant toxicity IFN-α and IL-12 did not come to general use 13,14.

There are promising results of studies on unmethylated cytosine-guanine dinucleotides, known as CpG motifs. These motifs, as the adjuvant to immunotherapy, promote Th1 response, preventing tissue eosinophilia and reducing IgE production, and bronchial hypersensitivity. IL-18 also appears to play complex role in up-regulating Th1 response 15. Although there is no certainty whether stimulating of Th1 response is beneficial in any case of allergic disease.

Recently most research is focused on down-regulation of Th2 immune response. The inhibition of eosinophil accumulation in asthma therefore represents a potential therapeutic strategy. Evidence from research showing IL-5 tissue localization in allergic diseases together with studies in IL-5-knockout, transgenic mice, suggest IL-5 is crucial to the development and release of eosinophils from the bone marrow and their enhanced adhesion to endothelial cells and their activation and secretion in the tissues. The presence of tissue eosinophils is evident feature of several allergic diseases including asthma, rhinitis, eosinophilic esophagitis and idiopathic hypereosinophilic syndrome 13,42.

Both IL-4 and IL-13 are very important cytokines for the tissue accumulation of eosinophils and they are main factors of IgE synthesis by B lymphocytes. Both exert their effects through the special receptor complex (IL-4Rα/IL-13Rα1) which then activates the transcription factor STAT-6. It has an important role in activating genes associated with the differentiation of naive T-cells into Th2 cells, airway inflammation, and bronchial hyperreactivity. Studies with soluble IL-4R given in a nebulized form demonstrated an improvement in the course of moderate asthma. However, despite these promising findings subsequent trials have not been as successful and consequently this treatment is no longer being developed 14,43. Airway hyper-reactivity is associated with the up-regulation of eotaxin and IgE production and eosinophil recruitment are regulated by IL-13. Many recent studies are focused on blocking action of IL-13 with promising results 43,44. IL-33 belongs to the IL-1 family. IL-33 and its receptor ST2 promote various activities related to the up-regulation of Th2 response. This cytokine is released predominantly by damaged cells. It suggests that IL-33 function as an endogenous danger signal particularly in epithelial and endothelial cells is directly exposed to environmental challenge. The experimental models of asthma revealed that the blockade of IL-33 and its receptors reduces the severity of the disease 45.

TNF-α is one of the most important cytokines in innate immune response that has been implicated in several chronic inflammatory diseases including also autoimmune disorders. Anti-TNF-α therapy proving useful in these conditions. TNF-α is produced by macrophages and other pro-inflammatory cells including dendritic cells, monocytes, B and T lymphocytes, neutrophils and what important for pathogenesis of allergic diseases by mast cells and eosinophils, which together with the structural cells including fibroblasts, epithelial cells, and smooth muscle cells represent significant sources of this mediator. TNF-α stimulates eosinophilic and neutrophilic cells and may play a key role in amplifying airway inflammation through activation of transcription factors: NF-κB and AP-1. Because TNF-α is thought to be the main mediator contributed to bronchial hyperreactivity, airway remodeling, and resistance to steroids in asthma and atopic dermatitis therefore represents a potential target for therapy 7,25,46.

Receptor for IL-17 (very important proinflammatory cytokine) has become the newest target for immunomodulatory drugs 47,48. For recent years attention of researchers is focused on the chemokine receptors, especially CCR3. Chemokines are a family of small, secreted proteins that control migration of many cells. Eotaxin is an inducible chemokine secreted in asthma that promotes selective recruitment of eosinophils from the blood into inflammatory tissues via CCR3, a seven-transmembrane-spanning G protein-coupled receptor.

Another approach to immunomodulation is targeting transcription factors. Attempting to modulate STAT-6 or GATA-3 and the signaling pathways may be essential to modification of the course of inflammation. But it presents serious challenge to researchers because these molecules are intracellular 49.

IgE plays a very important role in the pathogenesis of diseases associated with immediate hypersensitivity reactions, including allergic asthma, atopic dermatitis, urticaria, food allergies and others. IgE-dependent symptoms are a result of it binding to high-affinity receptors (FcεRI) on mast cells and basophils and low-affinity receptors (FcεRII) on macrophages, dendritic cells, and B lymphocytes. Allergen mole-
numerous clinical studies. Whereas in non-alergic asthma the airway inflammation is triggered by complex mechanisms, probably also involving IgE and perhaps, autoimmunity 7,8. In the past, various, potentially immunosuppressive drugs such as methotrexate, ciclosporine, gold salts and troleandomycin, have been used in patients with severe steroid-dependent or steroid-resistant asthma. None of these drugs gave significant steroid-sparing effects. However numerous adverse events during the therapies were observed. Many studies have failed to demonstrate an unacceptable risk-benefit ratio 7,9. GINA report does not recommend these therapies. A significant reduction in number of exacerbations was observed in patients with severe, non-eosinophilic asthma. Although chronic therapy with macrolides is associated with the risk of population antimicrobial resistance, than it should be reserved to special selected cases 51.

Humanized murine anti-TNF-α antibody - infliximab and soluble TNF-α receptor linked to human IgG3-etanercept have been developed and preliminary clinical studies in asthma showed significant improvements in lung function, reduction of airway hyperreactivity, and number of exacerbations, particularly in patients with severe asthma refractory to treatment with glucocorticosteroids 51. There were few attempts of treatment with both of these drugs the patients with atopic dermatitis, but without the expected success 52. However, a following clinical trial with the anti-TNF-α biologic golimumab in patients with severe, uncontrolled asthma reported negative clinical findings. Moreover, this study was terminated early due to unacceptable adverse events including frequent serious infections and eight cases of malignancies in the active-treatment group compared with the placebo group 46.

Omalizumab is a humanized monoclonal antibody directed to the FcεRI binding domain of human IgE resulting in a rapid decline in circulating levels of unbound IgE. Omalizumab does not bind to IgE bound to specific receptors on cells but down-regulates expression of high-affinity receptors by these cells. Omalizumab inhibited early-phase and late-phase allergen-induced asthmatic reactions and reduced serum free IgE concentrations and has progressed through clinical development 48. In several studies omalizumab has been shown to be beneficial as an add-on therapy in very severe atopic asthma 51. Cyclosporine has been still used in chronic urticaria refractory to other therapies 53. Several studies have examined the therapeutic efficacy of macrolides in patients with asthma. Because of their pleiotropic effects: anti-inflammatory and immunomodulatory in addition to antibacterial there were trials of macrolides treatment with low-dose macrolides. The Azithromycin in Severe Asthma Trial has demonstrated efficacy and safety of this therapy. A significant reduction in number of exacerbations was observed in patients with severe, non-eosinophilic asthma. Although chronic therapy with macrolides is associated with the risk of population antimicrobial resistance, it should be reserved to special selected cases 53.

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during long-term therapy, although they can in- crease temporarily pending the initial phase of SIT. But the inhibition of the recruitment and activation of effector cells including mast cells, eosinophils, and basophils in the allergic respira- tory mucosa of the nose and bronchi seems to be more important. Data strongly suggest that these mechanisms are modified as a consequence of altered T-lymphocyte responses following high dose allergen exposure during immunotherapy. Immunotherapy also has been shown to induce a subset of T-regulatory cells with allergen-specific increas in the production of IL-10 and TGFβ. These cytokines inhibit T responses and reverse decreases in the production of IL-10 and TGFβ. These cytokines inhibit T responses and reverse increases in the production of IL-10 and TGFβ. These cytokines inhibit T responses and reverse.

The results of previous in vitro studies and an- imal models have indicated the promising develop- ment of novel compounds targeted at diverse as- pects of the inflammatory cascade underlying pathogenesis of allergic diseases such as asthma, atopic dermatitis, and chronic urticaria. The develop- ment of novel anti-inflammatory therapies for these disorders has proven to be for the most part disappointing; in particular, results from animal-based studies have been very misleading. Despite significant benefit and few adverse effects, the blockade of action of single cytokine or mediator, or receptor often result in partial efficacy only, and does not addresses all allergic population. Future investigations of alternative pathways of inflammation are needed. Moreo- ver identification of specific endotype of disease seems to be essential for adequate treatment.

Available data indicate the complexity of the allergic inflammation and the possibility of par- ticipation of the same components in both aller- gic and autoimmune diseases. Both types of dis- orders result from dysregulation of the immune system. Not only genetic factors but also environ- mental factors (eg, infections) have an impact for their development and course. The imbalance of Th1/Th2 pathways is one of the aspects of patho- genic mechanisms only. Recent studies revealed that the same types of cells (Treg, Breg) regulate both types of inflammation There are involved similar cytokines, antibodies and mediators. The newest studies have provided additional in- sights into the roles of Th1 cells, B cells and Treg cells as well as the considerable communication and commonalities between the complex signa- ling pathways. In addition, external factors may have influence to the immune response. Taking into account possession of disease, major or minor shift in the future of allergic diseases research should be to identify phenotypes that will ultimately lead to individualized medicine and patient-tailored treatment.

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