Mechanisms of allergic inflammation in bronchial asthma

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Abstract

Cellular and molecular mechanisms in allergic inflammation and their clinical significance, based on pathogenesis of bronchial asthma are presented.

Key words: *allergic inflammation, cytokines, mast cell, eosinophil, Th2 cell, bronchial asthma, bronchial hyperresponsiveness*

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A very complex mechanisms depending on inflammatory mediators are the background of allergic inflammation in airways. This is manifested by several phenomena like transudate, mucosal edema, increased secretion of mucus, changed viscosity of discharge, impairment of cilliary transportation and contraction of smooth muscles of bronchi. The above symptoms and shedding of respiratory epithelium lead to the obturation of bronchi, i.e. to impaired ventilation of airways due to the constriction of their lumen.

One may distinguish two phases of allergic inflammation:

- immediate-type allergic reaction, in which coupling of allergen to specific IgE bound to the high affinity receptor ($Fc_{\varepsilon}RI$) on membrane of mast cells leads to the release of mediators including histamine, leukotrienes, prostaglandins, platelet activating factor and eosinophil chemotactic factor;
- late reaction, in which an afflux of inflammatory cells to bronchi and infiltration of subepithelial mucosa with eosinophils, lymphocytes (predominantly Th2) and mastocytes occurr. This phenomenon takes place following prior activation of cells and their migration to the inflammation site that i.e. towards the highest concentration of chemotactic factors. In this phase the most significant part in development and intensity of inflammatory response have cytokines released from cells and inflammation mediators secreted secondarily uder influence of cytokines.

Lasting inflammatory process is responsible for characteristic to asthma **bronchial hyperreactivity**, that is an exaggerated tendency to react with bronchospasm under influence of different stimuli. Bronchial asthma, due to chronic allergic inflammation, leads to the structural changes within bronchial walls. This process, called **remodeling**, is based on accumulation of collagen III and V, fibronectin and tenascin [1] in subepithelial layer instead of typical proteins like collagen IV and laminin, on hyperplasia and hypertrophy of goblet cells, submucosal glands, smooth muscles and an increase in number and volume of blood vessels [2–4]. Numerous cytokines and growth factors participate in phenomenon of remodeling with recent attention turned to IL-1, IL-13 and epithelial growth factor (EGF) [5–7].

In consequence of this remodeling, due to thickening of bronchial walls and shortening of smooth muscles, an increase in **partially irreversible bronchial hyperreactivity** may develop. In addition, an increase in vascularization of airways, hypertrophy of goblet cells and mucus glands may lead to the formation of mucus casts blocking airways [8, 9].

Allergic inflammation is found on every degree of advancement of bronchial asthma, including epizodic one [10]. Histopathological examinations confirm infiltration of bronchi with eosinophils, mast cells or lymphocytes. The main effector cells are mastocytes and eosinophils, which under an influence of various factors release preformed in granules and newly synthetized mediators, leading to the development of chronic inflammation. Lymphocytes,

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macrophages and epithelial cells also participate in development of inflammatory process.

An initial stage of allergic inflammation occurring after first contact with an allergen is **an uptake and processing of inhalatory allergens** by antigen presenting cells (APC), which include macrophages, dendritic cells and B lymphocytes. APC have an essential part in emergence of inflammatory response, because T lymphocytes usually can not react to allergens without their help [11].

Antigen presentation consists of succession of phenomena of procession and proper recognition of an allergen associated with MHC particle on surface of APC. Processing of an external allergen consists of its degradation in cytoplasm by proteolytic enzymes to peptide fragments which bind to MHC II particles in cytoplasms and transportation of these class II complexes to a cell surface.

B lymphocytes function as APC through surface immunoglobulins, whereas macrophages through nonspecific receptors.

Dendritic cells appear to be the main APCs. They have permanent expression of MHC molecules and uptake an antigen by means of pinocytosis. They initiate proliferation of T lymphocytes causing an increase in number of antigen specific T cells. In lungs, dendritic cells are located above the basal membrane of respiratory epithelium, at the site where the contact with an inhaled allergen occurrs [12]. In patients with bronchial asthma the number of $CD^{+}1a$ and MHC II dendritic cells is higher than in healthy subjects [13]. It has been known recently that dendritic cells have a key part not only in the induction of primary immune response but also in development and maintenance of allergic inflammation [14, 15].

Epithelial cells, although usually do not function as APCs can be stimulated to an expression of MHC class II by IFN gamma and function as APCs [16]. These cells have also an expression of other molecules important for antigen presentation (CD40, B7 and ICAM-1) [17].

The phenomenon of an antigen presentation has a key importance to a character of late inflammatory response. In dependence on which cytokines released in the process have an influence on precursor T lymphocytes, antigen specific Th cells differentiate towards **Th1 or Th2**. The kind of cytokines released during presentation of an antigen may in part depend on its nature but the cause of differentiation of Th is not precisely known [15]. In healthy subjects, Th lymphocytes differentiate mainly towards Th1 whereas in atopics towards Th2. It was shown that for differentiation towards Th2, the IL-4 is necessary whereas the one towards Th1, requests IFNγ, IFNα and IL-12. The latter cytokines simultaneously inhibit development of Th2 lymphocytes. IFNγ and IL-12 are secreted by APCs and act directly on T lymphocytes and indirectly through stimulation of NK cells towards production of IFNγ.

It is considered recently that T lymphocytes have an essential part in the induction and maintenance of inflammatory state in bronchial asthma [18]. Majority of the functions of T cells depends on the production of different cytokines, chemokines and other mediators. Th1 cells produce IL-2, IL-12, IFNγ, IFNβ and Th2 – IL-4, IL-5, IL-6, IL-10, IL-13 and sometimes in a very small guantities IL-2 and IFN gamma. However, both types of cells synthetize IL-3, GMCSF and TNF alpha [16].

Th2 lymphocytes stimulate humoral response, because IL-4 and IL-13 are the main factors inducing an increase in production of **IgE** in response to allergen. For the synthesis of IgE, an interaction of CD 40 with a ligand of stimulated T cells is also necessary [19]. IL-4 is produced also by mast cells, NKs and basophils [20] whereas IL-13 by mastocytes and stimulated Th2 cells [21]. It has the capacity of switching the B cells towards production of IgE. Similarly to IL-4, IL-13 also increases an expression of CD23 and MHC II on B cells and monocytes. IL-13 ifluences, in a lesser degree, the trancription and switching the immunoglobulin production towards IgG4 and IgE [7]. Atopic subjects have a higher number of cells producing IgE than healthy ones. Moreover, an increase in IgE synthesis is influenced by IL-5 and IL-6 produced by Th2, whereas IL-12 produced by Th1 inhibits synthesis of IgE by peripheral blood mononuclears stimulated IL-4 [22]. The factors influencing the synthesis of IgE independently on T cells may be Epstein Barr, RSV, Parainfluenza and Influenza viruses which have the ability to direct B lymphocytes to the production of specific IgE antibodies [23]. Independently on viral infection, an increase in IgE concentration was found in serum and bronchoalveolar lavage (BAL) of allergic subjects [24].

Mastocyte is an effector cell in immediate allergic reaction. Mature mast cells are present only in tissues and are particularly numerous in those which come into contact with an external environment i.e. mucosa of airways. One may distinguish the two subpopulations of human mast cells: the one, containing tryptase, present mainly in mucous membranes, the other, containing tryptase and chymase, in connective tissue. Crosslinking of surface IgE by an allergen triggers a release of preformed mediators like histamine, synthesis of lipid mediators like leukotrienes (LTC4, LTD4, LTE4) and prostaglandins (PGD2). These mediators induce an early phase of allergy. Several hours later, cytokines (IL-4, IL-5, IL-6, IL-13, TNF alpha, GMCSF) and chemokines are released, enhancing an inflammatory reaction.

Histamine released from mast cell granules during immediate allergic reaction acts through their H1, H2 and H3 receptors. Stimulation of H1 recepors is instaneous and disappears early whereas H2 react more slowly and longer. In majority of proinflammatory activities of histamine participate H1 receptors causing the contraction of smooth muscles of bronchi, stimulation of afferent fibres of n. vagus

and sensory fibres C. The result of these activities is bronchial hyperreactivity being not only bronchospasm but also the release of acetylcholine (increase in tonus of bronchial walls) and substance P (neurogenic inflammation). In addition, histamine through H1 receptors induces production and release of nitric oxide (NO), prostacycline PGI2, shrinking of endothelial cells leading to increased vascular permeability and edema. In allergic rhinitis, stimulation by histamine the sensory, afferent C fibres causes sneezing, pruritus and edema of nasal mucosa whereas stimulation of n. vagus – rhinorrhea.

Cysteine leukotrienes (LTD4 and LTE4) induce prolonged bronchospasm, increase vascular permeability and chemotaxis of inflammatory cells, mostly eosinophils (LTD4) and neutrophils (LTC4), towards an inflammation site. It was shown that positive provocation test with LTE4 caused an increase in number of eosinophils in biopsies of bronchial mucosa. One has to consider that leukotrienes are produced by different cells depending on the phase of an allergic reaction. At early one, their source are mast cells, later – eosinophils. This was confirmed by Smith, who found that antagonists of CysLT-1 inhibit both early and late phase of an allergic reaction [25].

The **late phase of allergic reaction** is the stage in which the main part have eosinophils accumulating at the site of inflammation and the active proteins produced by them (MBP, ECP, EDN, EPO). An appearance of inflammatory cells is preceded by the following phenomena [23, 26]:

- association of leukocytes with vascular endothelial cells,
- rolling of cells along a vessel walls with participation of E-selectins,
- adhesion and stimulation of leukocytes determined by the presence of $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins,
- passing between endothelial cells and chemotaxis of leukocytes towards an inflammation site.

These sequential phenomena are the result cooperation between inflammatory and stimulated endothelial cells. Vascular endothelium, by the release of cytokines (IL-1, IL-8), leukotriene B4, PAT, NO and chemotactic factors, influences the activation of inflammatory cells and increases the expression of adhesion molecules [27].

Eosinophils are the main effector cells in allergic inflammation and determine the course of bronchial asthma [28, 29]. The increased accumulation of eosinophils in airways of asthmatics was shown following inhalatory allergen provocation or after innhalation of IL-5 [22, 29]. In mice genetically lacking IL-5, allergen provocation did not increase the number of eosinophils and hyperreactivity of bronchi to metacholine [30]. These results confirm the essential participation of eosinophils in development of bronchial reactivity [31], particularly that the experimental placing of MBP in bronchi led to their hyperreactivity and on the other hand the autopsy data of subjects who died due to asthma revealed MBP deposits in airways [32]. Concentration of MBP and EDN in bronchoalveolar lavage were higher in patients with symptomatic bronchial asthma than during remission of the disease. Busse et al. have shown that inflammation mediators, particularly MBP, can directly damage respiratory epithelium and in addition secondarily cause degranulation of mast cells [28, 33]. IL-5 is not the only factor stimulating an infiltration of airways. IL-1, TNF alpha and IL-4 binding to the surface receptors of endothelium induce the expression of adhesion molecules, necessary for infiltration with eosinophils.

Respiratory epithelium acts as a defence against an external environment. This include the production of mucus by goblet cells, production of surfactant, efficient cilliary transportation, production and release of inflammation mediators and expression of adhesion molecules participating in movement of inflammatory cells. It was found that the cells of respiratory epithelium of asthmatics during remission show an increased expression of surface ICAM-1 molecules in comparison to the epithelium of healthy subjects. This may explain the increased sensitivity of children with atopia to infections of upper airways, for it is known that ICAM-1 is the tissue receptor for rhinovirus [34, 35]. It has been shown recently that Th2 cytokines cause, in vitro, a marked increase in expression of surface ICAM-1. It has been also found that rhinoviruses cause further increase an expression of Th2-induced ICAM-1 molecules [36].

The airway epithelium exert effector functions, as epithelial cell synthesize and secrete mediators such as leukotriens (LTC4 and LTD4), prostanoids and cytokines (IL-α, IL-1β, IL-6, Il-8, TNFα, TNFβ, GM-CSF and Rantes) [37].

The presence of one of the isoforms of **nitric oxide synthetase (iNOS)** was detected on the surface of respiratory epithelium cells, smooth muscles, vascular endothelium and macrophages. It turned out that an increase in the expression of iNOS may appear after exposure to an allergen [38]. The expression of iNOS on bronchial mucous membrane is induced by proinflammatory cytokines (TNFα, IL-1β), manufactured by macrophages and IFN gamma, produced by Th1 lymphocytes [39]. In patients put through specific provocation test, after which late phase of allergic reaction occurred, an increased concentration of NO in exhaled air was observed, correlating with the decrease in FEV1 [38]. Action of **NO** depends on its concentration at the reaction site – in low concentrations it regulates the homeostasis of immunological, circulatory and respiratory system, in high – has proinflammatory and cytotoxic activity. NO can exacerbate innflammation through selective blocking of Th1 lymphocytes, shifting the Th1/Th2 balance and also acting directly or through toxic hydroxyl radicals, participating in shedding of epithelium in bronchial asthma [40].

In atopic asthma, Th2 are the main lymphocyte population in biopsy samples of bronchi and BALf [16]. Th2 cytokines promote allergy and the degree of activation of Th2, and in allergic asthma, directly correlate with the severity of symptoms [12].

In 2003, Willis-Karp et al. have published the hypothesis that IL-13, produced by Th lymphocytes, eosinophils and mastocytes, induces bronchial hyperreactivity via its direct action on bronchial epithelium and smooth muscles and not in dependence on IgE and eosinophils. According to the hypothesis, bronchial hyperreactivity develops on basis of following events caused by IL-13:

- influencing respiratory epithelial cell it increases mucus production and impaires cilliary transportation, leading to obturation of airways,
- induces secretion of TGF beta by epithelial cells which stimulates secretion of extracellular matrix components and the mediators influencing matrix in bronchial walls,
- decreases the production of NO by epithelial cells, what probably leads to an increase in bronchial smooth muscles tonus,
- can induce production of anaphylatoxin, the complement component paticipating in development of bronchial hyperreactivity,
- can directly damage beta adrenergic receptor responsible for relaxation of bronchial smooth muscles [7].

The presented data prove how complicated and dependent on various factors is allergic inflammation in bronchial asthma. As it is known, this process is a result of numerous interactions of leukocytes, epithelial and endothelial cells regulated by cytokines, adhesion molecules, chemotactic and growth factors. The results of many investigations have therapeutical implications. Employment of glucocorticosteroids, inhibitors of leukotriene receptor, inhibitors of phosphodiesterase controls several links of allergic inflammation and this way influences the decrease or withdrawal of disease symptoms. Nevertheless, none of these drugs is able to stop the emergence of IgE dependent allergic reaction and subsequent inflammation. Recently, obtaining monoclonal antibodies to IgE created the possibility of blocking this reaction by inhibiting the IgE synthesis. An attempts of employment of the ”humanized” anti IgE antibody (Omalizumab) to the therapy of allergic diseases showed the decrease in concentration of serum IgE, bronchial hyperreactivity and the number of eosinophils in sputum [41, 42]. However, this therpeutical approach still requires further observation.

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