Cytokines and Bronchial Asthma

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ABSTRACT

A number of cytokines, including IL-1β, IL-6, IL-11 and tumor necrosis factor-α (TNF-α), having multifunctional capacities to initiate and amplify inflammatory processes are synthesized and released by bronchial epithelial cells.

There is preliminary evidence that early institution of anti-inflammatory therapy might lead to disease modification and limit the progression of sub-epithelial fibrosis and airway remodeling. The pathogenesis of asthma clearly involves many cells and mediators although the contribution of each individual factor is probably different from patient to patient depending on the setting and stimuli. Very recent finding of release of serum IL-4 between 1-2 hrs after exercise in asthmatics suggest that cytokines may also be involved in exercise-induced bronchospasm.

It is hoped that rapid progress in the area of asthma genetics and pharmacogenetics will yield more precise and patient-specific understanding of asthma pathogenesis and allow practitioners to prescribe therapies that are designed for a particular patient or exacerbation.

INTRODUCTION

Bronchial asthma is a chronic inflammatory disorder characterized by episodic hyper-responsiveness. Lately it has been demonstrated that bronchial asthma is a generalized inflammation involving GI tract.¹

Asthma is a chronic inflammatory disorder of the airway. Eosinophilic inflammation is a feature of asthma. Serological markers such as serum eosinophilic cationic protein can be used as a predictive marker for asthma exacerbation in patients with persistent asthma.² However, in recent years, various cytokines and chemoattractants have been increasingly involved in allergic inflammation and bronchial asthma.³

Several studies have demonstrated that bronchial epithelial cells are a rich source of a large variety of cytokines, therefore suggesting that they may play an important modulatory role in airway disease. Indeed more recent evidence suggests that epithelial cells of patients with and without respiratory disease may be different with regards to their reactivity to inhaled irritants and different types and quantities of cytokines they synthesize and release.⁴ Recently, it has been reported that proallergic cytokine particularly IL-4, IL-13 secreted by Th2 cells are key regulators of IgE synthesis playing major role in atopic asthma.⁵⁻⁷ Still recently IL-9 has been involved in the inflammatory process of bronchial asthma.⁷ It has been demonstrated that IL-9 a pleiotropic activities on various cell types plays an important role in pathogenesis of asthma. Unlike other cytokines such as IL-4, IL-5, IL-9 seems to primarily enhance the activities of other cytokines and factors. This might be important in terms of antagonizing IL-9 activity. Blocking IL-9 may be less likely to compromise normal host defense than the blockade of other cytokines.⁸

CYTOKINES AND INTERLEUKINS

Cytokines are glycoproteins that are synthesized and released by a variety of cell types in response to varied stimuli. Included among cytokines are interleukins (presently numbering over 30), interferons, growth factors and others. Interleukin is a collective term for group of structurally and functionally distinct proteins secreted by different types of leukocytes that are involved in cell to cell communication. A factor is classified as an interleukin if its primary structure is known and the factor has been characterized biochemically. The interleukins have a variety of functions, but most are involved in directing other immune cells to divide and differentiate. Each interleukin acts as a specific limited group of cells that express the correct receptor for that interleukin. Major source and the effects of major interleukins have been shown in Table 1.

MEDIATORS INVOLVED IN ASTHMA

Several studies have demonstrated that bronchial epithelial cells synthesize and release a variety of different classes of pro-inflammatory mediators including nitric oxide endothelins, metabolites of arachidonic acid and cytokines.⁹ However, the production of pro-inflammatory cytokines by the airway...
epithelium has been of particular interest in allergic conditions such as asthma and allergic rhinitis which influence the activity of inflammatory cells such as eosinophils, T lymphocytes, macrophages, dendritic cells and neutrophils. Furthermore, structural cells (e.g. epithelial cells, fibroblasts and smooth muscle cells) have also been recognized as potential contributors to ongoing inflammation and injury.  

Bronchial epithelial cells have been shown to generate a number of different chemotactic cytokines including lymphocyte chemoattractant factor, granulocyte macrophage colony stimulating factor (GM-CSF) and the chemokine superfamily (α or C-X-C and β or C-C). Recent tools of investigating airway obstruction using fibrooptic bronchoscopy, bronchodilator lavage endoscopy as well as noninvasive studies such as sputum and exhaled breath condensate have contributed further evidence of various inflammatory cells and mediators to airway inflammation in asthma.

More recently, it has been shown that bronchial epithelial cells release the C-C chemokines RANTES (regulated on activation normal T-cell expressed and secreted) and monocyte chemotactic protein - 1 (MCP-1).  

**CELLULAR INFLAMMATION AND CYTOKINE RELEASE**

**Mast cells**

The mast cell is a key player in the early allergic response that typically starts within minutes of exposure to an appropriate antigen. When exposed to an adequate dose of antigen, allergic asthma patients develop acute symptoms (coughing, wheezing and dyspnoea). These symptoms peak within 10-15 minutes and typically resolve within 60 minutes of the exposure. The mast cell surface bound IgE is cross-linked by the antigen, leading to mast cell activation and release of potent mediators such as histamine, leukotrienes, prostaglandin D2, thromboxane B2 and platelet activating factors resulting in airway smooth muscle contraction, edema and enhanced mucous secretions that lead to airflow limitations and the manifestations of acute asthma symptoms.

There is evidence that the mast cells may also contribute to ongoing airway inflammation through the release of cytokines (IFN-α, IL-1, IL-4, IL-5, IL-6, IL-8, IL-16) and chemokines (MIP-1α, MIP-1β, MCP and RANTES).  

Allergic response starts with antigen sensitization in which an antigen presenting cell digests antigen and presents it to T cell, with subsequent differentiation in Th2 cell capable of generating various cytokines (Fig. 1). Through the release of these factors, the mast cells could conceivably contribute not only to the acute allergic response but also to the persistence of airway inflammation and occurrence of late phase response. However, there is also evidence of ongoing release of histamine that is associated with increased airway responsiveness and obstruction in asthma, probably released by basophil.  

**Eosinophils**

Eosinophils are closely linked to allergic diseases often present in airway allergic asthmatics and correlate with parameters of disease severity. These cells contain potent mediators in their granules including major basic protein eosinophil cationic protein, eosinophil-derived neurotoxin and eosinophil peroxidase (Fig. 1) causing airway hyper-responsiveness.  

Typically the eosinophils are recruited to the airway a few hours after an allergen is inhaled and can persist for 2 to 4 weeks there after. However, their maturation, activation and recruitment to the airway are strongly influenced by IL-5. Levels of IL-5 are increased in blood and BAL fluid of allergic asthma subjects especially following allergen challenge and that monoclonal antibody against IL-5 dramatically reduced circulating and sputum eosinophils. However, exercise-induced bronchoconstriction does not cause eosinophilic airway inflammation or airway hyper-responsiveness.

In antigen challenge model in which eosinophils are predominant cells, the neutrophils are recruited to the airway before eosinophils and they are a prominent cell within 6 hours after the challenge. Interestingly, the numbers of neutrophils seen 6 hours after local allergen challenge correlate with the level of IL-8 in BAL fluid suggesting that this cytokine plays an important role in this process.  

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<th>Table 1: Effects of Interleukins (IL)</th>
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<td><strong>Major source</strong></td>
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role in neutrophil recruitment to the airway and neutrophils have been increasingly involved with severity and persistent asthma.¹²

**Lymphocytes**

There has been special emphasis on a T cell subset, the Th2 type, that secretes cytokines as IL-4, IL-5 and IL-13³³ because these cells are increased in bronchoalveolar lavage fluid of atopic asthmatics²⁶,³⁴ and increase further following the introduction of an allergen (Fig. 1).³⁵

Levels of IL-5 correlate with number of BAL eosinophils obtained after antigen challenge in allergic and asthmatic subjects.¹⁹,³⁶ The T cell is also capable of producing numerous chemokines and cytokines that contribute to up regulation of other inflammatory cells and worsening of acute and chronic inflammation.

**Macrophages**

Macrophages are predominant resident cells in the lower airways and can up-regulate the inflammatory response by generations of cytokines such as GM–CSF, IL-1, IL-6.³⁷ Macrophages also generate anti-inflammatory cytokines as IL-10, IL-12 and TGF-β.

**Epithelial cells and fibroblast**

While epithelial cells and fibroblasts are traditionally viewed as structural cells, they are being increasingly recognized for their ability to contribute to airway inflammation and injury by release of cytokines and chemokines in addition to matrix proteins (elastin, fibronectin, laminin and collagen).²⁸,³⁹

**AIRWAY REMODELING**

It is now recognized that structural airway changes are present not only in severe fatal asthma, but also in mild to moderate versions of the disease. Expression of TGF-β in airway mucosa correlates with disease severity and the degree of sub-epithelial fibrosis.⁴⁰ Finally, expression of another cytokine, IL-11 is increased in airway mucosa of patients with moderate to severe compared with mild asthma.⁴¹ This suggests that it may play a role in the development of airway remodeling.

**CYTOKINES AND EXERCISE-INDUCED BRONCHOSPASM**

Exercise-induced bronchospasm (EIB) is common in children but recent studies show adults are equally involved⁴² and atopy plays an important role in development of EIB⁴³ and that proallergic cytokines particularly IL-4 and IL-13 secreted by Th2 cells are key regulators of IgE syntheses playing major role in atopic asthma.⁴⁴ Higher IL-4 has been demonstrated in BAL fluid of asthmatic subjects.⁴⁵ It has been reported that use of monteleukast (leukotriene receptor antagonist) in asthma reduces serum level of IL-4.⁴⁶ Very recently, it has been demonstrated that blood level of IL-4 rises during exercise-induced bronchospasm.⁴⁷

**REFERENCES**

5. Koh YI, Choi IS, Lim H. Atopy may be related to exercise induced bronchospasm in asthma. *Clin Experimental Allergy* 2002;32:532-36.