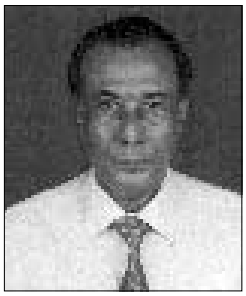

Cytokines and Bronchial Asthma

HL Dhar

Director, Medical Research Centre, Bombay Hospital Trust, Mumbai 400 020.

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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.[3,5-7] 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

Table 1: Effects of Interleukins (IL)

	Major source	Major effects
IL-1	Macrophages	Stimulation of T cells and antigen-presenting cells. B-cell growth and antibody production Promotes hematopoiesis (blood cell formation).
IL-2	Activated T cells	Proliferation of activated T cells.
IL-3	T lymphocytes	Growth of blood cell precursors.
IL-4	T cells and mast cells	B-cell proliferation. IgE production.
IL-5	T cells and mast cells	Eosinophil growth.
IL-6	Activated T cells	Synergistic effects with IL-1 or TNF-α.
IL-7	Thymus and bone marrow stromal cells	Development of T cell and B cell precursors.
IL-8	Macrophages	Chemoattracts neutrophils.
IL-9	Activated T cells	Promotes growth of T cells and mast cells.
IL-10	Activated T cells, B cells and monocytes	Inhibits inflammatory and immune responses.
IL-11	Stromal cells	Synergistic effects on hematopoiesis.
IL-12	Macrophages, B cells	Promotes T_H1 cells while suppressing T_H2 functions
IL-13	T_H2 cells	Similar to IL-4 effects
IL-15	Epithelial cells and monocytes	Similar to IL-2 effects.
IL-16	CD8 T cells	Chemoattracts CD4 T cells.
IL-17	Activated memory T cells	Promotes T cell proliferation.
IL-18	Macrophages	Induces IFN-γ production.

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.[9]

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[11,12] (α or C-X-C and β or C-C). Recent tools of investigating airway obstruction using fibrooptic bronchoscopy, bronchodilator lavage endoscopy[13] 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.[14]

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).[10,15]

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.[16] 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 D_2, thromboxane B_2 and platelet activating factors[17] 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).[18]

Allergic response starts with antigen sensitization in which an antigen presenting cell digests antigen and presents it to T cell, with subsequent differentiation in Th_2 cell capable of generating various cytokines (Fig. 1).

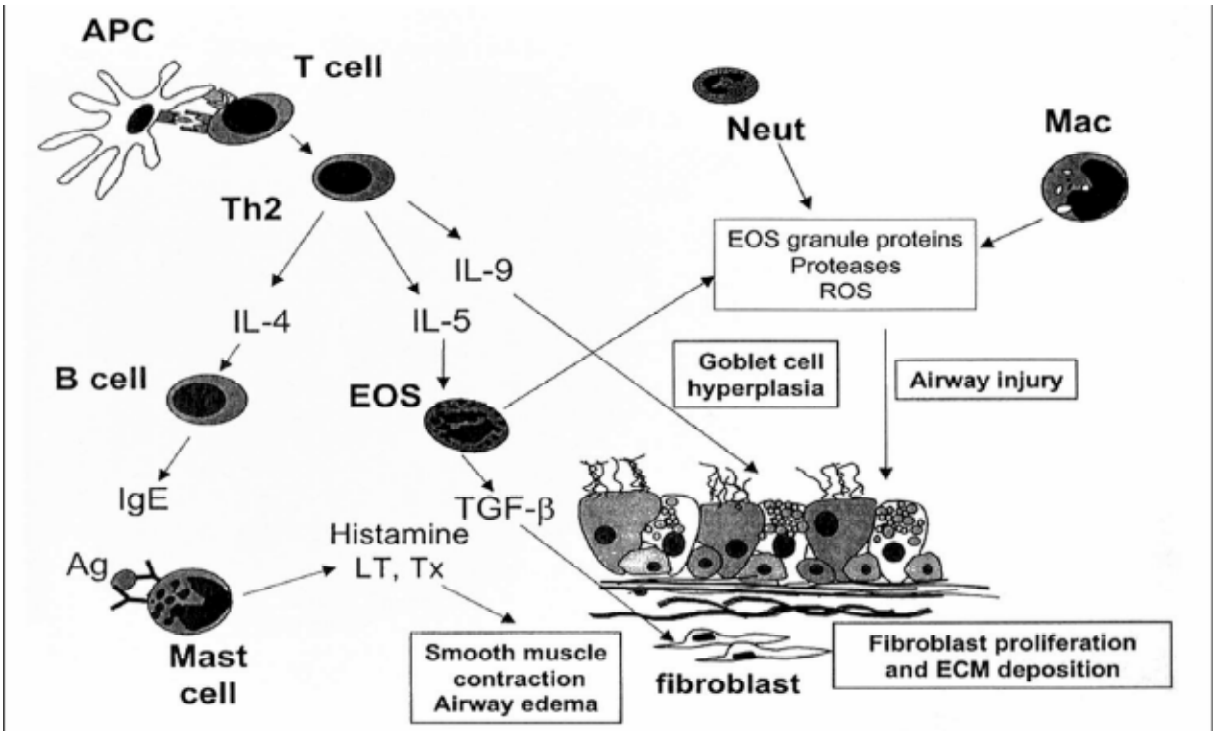
Through the release of these factors, the mast cells could conceivably contribute not only to the acute allergic response but also to the persistence of airway inflammation and occurrence of late phase response. However, there is also evidence of ongoing release of histamine that is associated with increased airway responsiveness and obstruction in asthma[19] probably released by basophil.[20]

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)[21] causing airway hyper-responsiveness.[22]

Typically the eosinophils are recruited to the airway a few hours after an allergen is inhaled[23] and can persist for 2 to 4 weeks there after.[24] However, their maturation, activation and recruitment to the airway are strongly influenced by IL-5.[25] Levels of IL-5 are increased in blood[26] and BAL fluid of allergic asthma subjects[27] especially following allergen challenge[19,28] and that monoclonal antibody against IL-5 dramatically reduced circulating and sputum eosinophils.[29] However, exercise-induced bronchoconstriction does not cause eosinophilic airway inflammation or airway hyper-responsiveness.[30]

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.[31] Interestingly, the numbers of neutrophils seen 6 hours after local allergen challenge correlate with the level of IL-8 in BAL fluid[32] suggesting that this cytokine plays an important



EOS : eosinophgil, LT : leukotrienes, Tx : thromboxanes, ROS : reactive oxygen species, Neut : neutrophil, Mac : macrophages, TGF - β : transforming growth factor β, ECM : extracellular matrix. *Med Clin N Am* 2002;86:925-936

Fig. 1: The spectrum of inflammatory responses

role in neutrophil recruitment to the airway and neutrophils have been increasingly involved with severity and persistent asthma.[32]

Lymphocytes

There has been special emphasis on a T cell subset, the Th2 type, that secretes cytokines as IL-4, IL-5 and IL-13[33] because these cells are increased in bronchoalveolar lavage fluid of atopic asthmatics[26,34] 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).[38,39]

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 involved[42] and atopy plays an important role in development of EIB[43] 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

1. Wallaert B, Camblin C, Tsicopoulo A, et al. Asthma – more than a bronchial disease. *ACI International* 2000;12:161-65.
2. Sorknen C, Mc Gillk, Busse WW. Evaluation of serum eosinophil cationic protein as a predictive marker for asthma exacerbation in patients with persistent disease. *Clin Exp Allergy* 2002;32:1355-59.

3. Romagnani S. Cytokines and chemoattractants in allergic inflammation. *Mol Immunol* 2002;38:881-885.
4. Mills PR, Davies RJ, Devalia JL. Cytokine release from bronchial epithelial cells. *ACI International* 2000;12:122-23.
5. Koh YI, Choi IS, Lim H. Atopy may be related to exercise induced bronchospasm in asthma. *Clin Experimental Allergy* 2002;32:532-36.
6. Pawankar R. Anti-IgE treatment in allergic disease. *ACI international* 2001;13:4-10.
7. Akpinarli A, Gue D, Kalayachi O, et al. Increased interleukin 4 and decreased interferon gamma production in children with asthma: function of atopy or asthma. *J asthma* 2002;39:159-65.
8. Hauber HP, Tulic MK, Hamid Q. IL-9 and asthma. *ACI International* 2003;15:119-25.
9. Mills PR, Davies RJ, Devalia JL. Cytokine release from bronchial epithelial cells. *ACI International* 2000;12:122-25.
10. Holgate ST, Davies DE, Lakie PM, et al. Epithelial mesenchymal interactions in the pathogenesis of asthma. *J Aller Clin Immunol* 2000; 105:193-204.
11. Schall TJ. Biology of the RANTES/SIS cytokine family. *Cytokine* 1991;3:165-83.
12. Miller MD, Krangel MS. Biology and biochemistry of the chemokines. A family of chemotactic and inflammatory cytokines. *Crit rev Immunol* 1992;12:17-46.
13. Jarjour NN, Peters SP, Djukanovic R, et al. Investigative use of bronchoscopy in asthma. *Am J Respir Crit Care Med* 1998;157:692-7.
14. Gibson PG, Henry RL, Thomas P. Noninvasive assessment of airway inflammation in children: Induced sputum, exhaled nibicoxide and breath condensate. *Eur Resp J* 2000;16:1008-15.
15. Sousa AR, Lane SJ, Nakhosteen JA, et al. Increased expression of monocyte chemoattractant protein 1 in bronchial tissue from asthma subjects. *Am J Respir Cell Mol Biol* 1994;10:142-47.
16. Pearlman DS. Pathology of the inflammatory response. *J Aller Clin Immunol* 1999;104:s132-7.
17. Schwartz LB. Mast cells and basophils. *Clin Allergy Immunol* 2002;16: 3-42.
18. Bissonnette EY, Befus AD. Mast cells in asthma. *Canadian Respir J* 1998; 5:23-4.
19. Jarjour NN, Sedgwick JB, Swensen CA, et al. Lale allergic airway response to segmental bronchopulmonary provocation in allergic subjects is related peripheral blood basophil histamine release. *J Aller Clin Immunol* 1997; 99:89-93.
20. Nouri-Aria KT, Irani AM, Jacobson MR, et al. Basophil recruitment and IL-4 production during human allergen induced asthma. *J Aller Clin Immunol* 2001;108:205-11.
21. Gleich GJ. Mechanism of eosinophil associated inflammation. *J Aller Clin Immunol* 2000;105:651-63.
22. Gleich GJ. Logering DA, Fujiswa T, et al. The eosinophil as a mediator of damage to respiratory epithelium: a model for bronchial hyperreactivity. *J Aller Clin Immunol* 1988;81:776-81.
23. Gauvreau GM, Watson RM, O'Byrne PM. Kinetics of allergen induced airway eosinophilic cytokine production and airway inflammation. *Am J Respir Crit Care Med* 1999;160:640-7.
24. Shaver J, O'Connor J, Pollice M, et al. Pulmonary inflammation after segmental ragweed challenge in allergic asthmatic and non-asthmatic subjects. *Am J Respir Crit Care Med* 1995;152:1189-97.
25. Kotsimbos AT, Hamid Q. IL-5 and IL-5 receptor in asthma. *Mem Inst Oswaldo Cruz* 1997;92:75-91.
26. Corrigan CJ, Haczku A, Gemou, Eugesaeth V, et al. CD4 T-lymphocyte activation in asthma is accompanied by increased serum concentration of interleukin-5. Effect of glucocorticoid therapy. *Am Rev Respir Dis* 1993; 147:540-7.
27. Sur S, Gleich GJ, Swanson MC, et al. Eosinophilic inflammation is associated with elevation of interleukine-5 in the airways of patients with spontaneous symptomatic asthma. *J Aller Clin Immunol* 1995;96:661-8.
28. Surs, Kita H, Gleich GJ, et al. Eosinophil recruitment is associated with IL-5 but not RANTES, twenty hours after allergen challenge. *J Aller Clin Immunol* 1996;97:1272-8.
29. Leckie MJ, Ton Brinke A, Knan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils airway hyper-responsiveness and the late asthmatic response. *Lancet* 2000;356:2144-8.
30. Gail M, Gauvreau GM, Ronnen GM, et al. Exercise induced broncho-constriction does not cause eosinophilic airway hyper-responsiveness in subjects with asthma. *Am J Resp Crit Care Med* 2000;162:1302-07.
31. Nocker RE, Out TA, Willer FR, et al. Influx of neutrophil into the airway lumen at 4 h after segmental allergen in asthma. *Int Arch Allergy Immunol* 1999;119:45-53.
32. Basse WW, Banks Schlegel S, Wenzel SE. Pathophysiology of severe asthma. *J Aller Clin Immunol* 2000;106:1033-42.
33. Robinson DS. Th2 cytokines in allergic disease. *Br Med Bull* 2000;56: 956-68.
34. Humbert M, Durhana SR, Kimmitt P, et al. Elevated expression of messenger ribonucleic acid encoding IL-13 in the bronchial mucosa of atopic and nonatopic subjects. *Asthma J Aller Clin Immunol* 1997;99:657-65.
35. Kelly EA, Rodriguez RR, Busse WW, et al. The effect of segmental bronchoprovocation with allergen on airway lymphocyte function. *Am J Respir Crit Care Med* 1997;156:1421-8.
36. Sur S, Gleich GJ, Offord KP, et al. Allergen challenge in asthma; association of eosinophils and lymphocytes with interleukin 5. *Allergy* 1995;50:891-8.
37. Gosset P, Tillie Leblond I, Qudins, et al. Production of chemokines and proinflammatory and anti-inflammatory cytokines by human alveolar macrophages activated by IGE receptors. *Aller Clin Immunol* 1999;103: 289-97.
38. Polito AJ, Proud D. Epithelia cells as regulators of airway inflammation. *J Allergy Clin Immunol* 1998;102:714-8.
39. Redington AE, Sime PJ, Howarth PH, et al. Fibroblasts and the extracellular matrix in asthma. In: Holgate ST Busse WW editors. Inflammatory mechanisms in asthma. New York: Marcel Dekker, Inc. 1958;443-67.
40. Minshall EM, Leung DY, Martin RJ, et al. Eosinophil associated TGF-B1 mRNA expression and airways fibrosis in bronchial asthma. *Am J Respir Cell Mol Biol* 1997;17:326-33.
41. Minshall E, Chakir J, Laviolette M, et al. IL-11 expression is increased in severe asthma: association with epithelial cells and eosinophils. *J Aller Clin Immunol* 2000;105:232-8.
42. Pargaonkar KA, Dhar HL. Evaluation of exercise induced asthma (EIA)-effects of various drugs. A double blind cross over study. Advances in asthmology. *Excerpta Medica* 1991;958:569-575.
43. Joshi SV, Dhar HL. Synopsis of PhD thesis. Allergenicity of mite – Dermatophagoides species and its clinico-immunological significance in exercise induced bronchospasm. University of Mumbai 2004.
44. Walker C, Bade E. Allergic and nonallergic asthmatics have distinct patterns of T cell activation and cytokine in peripheral blood and bronchoalveolar lavage. *Am Rev Respir Dis* 1992;146:109-115.
45. Leff JA, Busse WW, Pearlman DS, al. Monteleukast, a leukotriene receptor antagonist for the treatment of mild asthma and exercise induced broncho-constriction. *New E J Med* 1998;339:147-52.
46. Stelmach I, Jerzynska J, Kuna P. A randomised double blind trial of the effect of treatment with monteleukast on bronchial hyper-responsive and serum eosinophillic cationic protein (ECP), somble interleukin 2 receptor (S IL-2R), IL-4 and soluble intercellular adhesion molecule 1 (s1cAM-1) in children with asthma. *J Aller Clin Immunol* 2002;109:257-63.
47. Joshi SV, Dhar HL. House dust mite sensitivity, Interleukin-4 and exercise induced bronchospasm. *JAPI* 2004 (Submitted).