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Review

Immunity and asthma: friend or foe?

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SUMMARY

Immunity is responsible for the defense mechanism of the body but in case of autoimmune diseases, its role gets diverted. Like so many other diseases, asthma is also considered as one of the most common autoimmune diseases to be occurring in community. Asthma is defined as a chronic inflammatory airway disease that is characterized by airway hyper reactivity and mucus hypersecretion that result in intermittent airway obstruction. The incidence of allergic asthma has almost doubled in the past two decades. Although, precise causative mechanism of asthma is unknown, but several mechanisms have been proposed that is immunological, pharmacological and genetic mechanisms, and airway and neurogenic inflammation. The inflammatory process observed in the asthmatic patients is the final result of a complex network of interactions between various immunological cell lineages, its mediators and secreted substances. Thus, among the mechanisms proposed, the immunological one plays a key role. Through this article, we have tried to provide some insight into immunological mechanisms in pathogenesis of asthma.

Keywords: Asthma; Cytokines; Immunity; Inflammation

INTRODUCTION

Asthma is a chronic inflammatory disorder of the respiratory airways, characterized by increased mucus production and airway hyper-responsiveness resulting in decreased airflow, and marked by recurrent episodes of wheezing, coughing and shortness of breath (Alen, 2001). The incidence of allergic asthma has almost doubled in the past two decades (Doockson, 1999; Umetsu *et al.*, 2002). In United States, the current overall prevalence in children is estimated at 6 - 7.5%, with a total of over 5 million children affected. Thus, asthma is fourth-leading cause of disability in children, and one of the most common reasons for school absenteeism. India has an estimated 15 - 20 million asthmatics. Approximately 5,000 people die each year due to asthma. Present cost of care for asthmatics being estimated at about 6 billion US $ per year (Doockson, 1999; Alen, 2001).

The pathophysiologic hallmark of asthma is a reduction in airway diameter brought about by contraction of smooth muscle, vascular congestion, edema of the bronchial wall, and thick, tenacious secretions. The net result is an increase in airway resistance, a decrease in forced expiratory volumes and flow rates, hyperinflation of the lungs and thorax, increased work of breathing, alterations in respiratory muscle function, changes in elastic

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recoil, abnormal distribution of both ventilation and pulmonary blood flow with mismatched ratios, and altered arterial blood gas concentrations. Thus although asthma is considered to be primary a disease of airways, virtually all aspects of pulmonary function are compromised during an acute attack (McFadden, 2003). The gross pathology of asthmatic airways displays lung hyperinflation, smooth muscle hypertrophy, lamina reticularis thickening, mucosal edema, epithelial cell sloughing- the 'Creola bodies', cilia cell disruption, and mucus gland hypersecretion. Microscopically, asthma is characterized by the presence of increased numbers of eosinophils, neutrophils, lymphocytes, plasma cells, Charcot-Leyden crystals (eosinophillic proteins), and Curschman's spirals (eosinophils + mucus), in the bronchial tissues, bronchial secretions, and mucus. Thus, the inflammatory process observed in the asthmatic patients is the final result of a complex network of interactions between various cell lineages, its mediators and secreted substances (McFadden, 2003).

A pattern of behavior of the inflammatory response that leads to the final went of bronchospasm is observed and divided into two phases. The first, called immediate reaction is caused by the release of mediators by mast cells, on a hyperresponsive smooth muscle after contact of the inhaled antigen with the sensibilized airway. It reaches the pick of activity around 20 - 30 min subsequently to inhalation. The second one, called late reaction, provoked by the release of chemotactic-cytokines responsible for the attraction of the main inflammatory cells like eosinophils, Th2 lymphocytes, neutrophils, and monocytes from the systemic circulation to the sensibilized airways. Then it happens a new triggering of the immune cascade and more bronchospasm.

Even if precise causative mechanism of asthma is unknown, several mechanisms have been proposed that is immunological, pharmacological and genetic mechanisms, and airway and neurogenic inflammation but here we specifically focus on the immunity in development and progression of asthma.

Immunological mechanism

Among the mechanisms proposed in the pathogenesis of asthma, the immunological one play a key role.

An agent which causes asthma may be considered as 'inducer' (that is causing reversible airway bronchoconstriction associated with long-lasting airway hyperresponsiveness to nonspecific &/or specific agents) or as 'inciter' (that is triggering asthma attacks) (Dolovich and Hargreave, 1981).

Active asthma is characterized by the presence of airway inflammation (Editorial, 1991). Asthmatic inflammation is differentiated into three broad categories: acute, subacute, and chronic. Acute asthmatic inflammation involves the early recruitment of cells into the airway, while subacute asthmatic inflammation is characterized by the activation of recruited and residual effector cells in incessant inflammation. Chronic asthma is defined by constant inflammation leading to cellular damage, which in tern activates cellular repair (King, 1999).

Complex cellular and molecular interactions cause airway inflammation in asthma. The type of inflammatory infiltrate depends on specific events, including the nature and activities of the specific adhesion molecules expressed by the endothelium and by blood leucocytes, as well as the release of chemotactic factors, which cause migration of cells in tissue. The ensuing inflammation amplifies an individual hypersensitivity reaction by recruitment of other cells and perpetuates the clinical symptoms (King, 1999). Most popular hypothesis at present for the pathogenesis of asthma is that it derives from a state of persistent sub acute inflammation of airways. More recent studies have found substantial inflammation in bronchial-biopsy specimens from patient with asthma, even those with mild disease. These inflammatory changes can occur throughout the central (Haley *et al*., 1998) and peripheral (Kraft *et al*., 1996; Haley *et al*., 1998) airways and often vary with the severity of the disease (Vignola *et al*., 1998; Hamid and Minshall, 2000). Although not

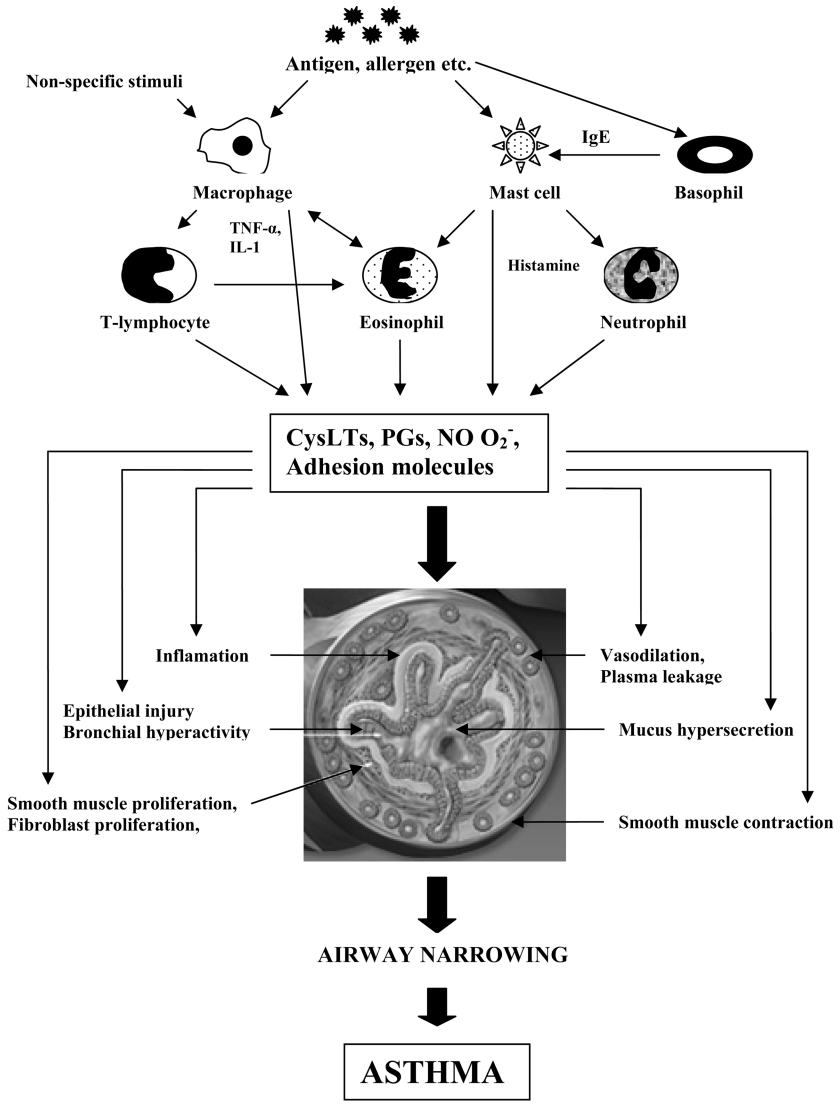

Fig. 1. Role of immune cells in pathogenesis of asthma.

observed uniformly, denudation of the airway epithelium, deposition of collagen beneath the basement membrane, mast cell degranulation, and infiltration of the airway by lymphocytes and eosinophils have been found in patients with mild-to-moderate asthma.

Many of the cells of immune system in the airway appear to be activated, implying that by releasing preformed or newly synthesized mediators, they have a direct role in asthma (Fig. 1) (William *et al.*, 2001). The cells thought to play important parts in the inflammatory response are mast cells, eosinophils, lymphocytes, and epithelial cells. The roles of neutrophils and macrophages are less well defined. Each of these cell types contributes mediators and cytokines to initiate and amplify both inflammation and long term pathologic changes. The mediators released- histamine, bradykinine, the leukotrienes C, D, and E, platelet activating factor, and prostaglandins PGE_2, $PGF_{2\alpha}$, and -D_2 produce an

intense, immediate inflammatory reaction involving bronchoconstriction, vascular congestion and edema. This intense local event can then be followed by a more chronic one. The chemotactic factors elaborated (eosinophils and neutrophil chemotactic factors of anaphylaxis and leukotriene B4) bring eosinophils, platelets and neutrophils to the site of the inflammation. These infiltrating cells as well as resident macrophage and airway epithelium itself potentially are an additional source of mediators to enhance both the immediate and cellular phase. The airway epithelium is both the target of and a contributor to the inflammatory cascade. These cells amplify bronchoconstriction by elevating endothelin-1 and promoting vasodilation through the release of nitric oxide, PGE_2, and the 15-hydroxyeicosatetraenoic acid products of arachidonic acid metabolism. They also generate cytokines such as granulocyte-macrophage colony stimulating factor (GM-CSF), IL-8, RANTES and eataxin (McFadden, 2003). The presence of cytokines that mediate inflammation and chemotactic chemokines is observed in bronchoalveolar-lavage fluid or pulmonary secretions of asthmatic patients (Chung and Barnes, 1999). Since these cytokines and chemokines are elaborated by resident and inflammatory cells in airways and have many effects on these cells, a variety of autocrine, paracrine, and endocrine networks could participate in asthma. Some cytokines initiate inflammatory response by activating transcription factors, which are proteins that bind to the promoter region of genes. Transcription factors involved in asthmatic inflammation include nuclear factor-$_{\kappa}$B, activator protein-1, nuclear factor of activated T cells, cAMP response-element binding protein, and various members of the family of signal transduction-activated transcription (STAT) factors. These transcription factors act on genes that encode inflammatory cytokines, chemokines, adhesion molecules, and other proteins that induce and perpetuate inflammation. Corticosteroids modulate immunoinflammatory responses in asthma by inhibiting these transcription factors (Barnes and Adcock, 1998).

The molecular mechanisms underlying immune system activation for allergen induced asthma includes several components of immune response-immune related receptors, effector molecules, functional role of effector T cells, costimulatory molecules etc.

Receptors

There are three receptors linked to asthmatic pathogenesis: IL-1 receptor 1 (IL-1R1), the Toll-like Receptor (TLR) and CCR8. The cytokine IL-1 promotes the proliferation of Th2 cells and specific antibody responses. IL-1 also induces the expression of exotaxin, an eosinophil chemoattractant, on pulmonary epithelial cells. Schmitz *et al.* (2003), showed that, post allergen exposure, null IL-1R1 mice had reduced CD4+ T cell proliferation relative to wild type controls, IL-1R-/- mice also had limited pulmonary antibody responses, eosinophillia, and globlet cell mucus production due to impaired CD4+ Th2 function and development. These results, however, are for mild asthma model and a more severe asthmatic model with IL-1R1 null mutations did not alter the immune responses. The authors hypothesize, with data from concurrent studies, that IL-1 may play a role in T-cell priming through induction of Cd40L and OX40 receptor (Schmitz *et al.*, 2003). Another potential receptor involved in asthma responses is the Toll-like Receptor (TLR). There are currently 10 known isoforms (TLR 1-10). The reactivity and activation of TLR's with host protein suggests a functional role in inflammatory states and autoimmune responses. For example, 'the hygiene hypothesis' proposes that fewer bacterial infections in industrialized and modernized nations are inversely proportional to the incidence of allergic diseases. Since bacterial infections mount Th1 responses through various TLRs, it is possible that a reduction in TLR ligand on pathogens coupled to allergen exposure means a reduction in shifts from

a Th2 to Th1 immune response for hypersensitivity reactions. This also suggests that activating TLR receptors in conjunction with allergen may be necessary to induce immune deviation (Heine *et al.*, 2003). Th2 and Th1 CD4+ cells show differential receptor expression indicative of the different effector and recruitment mechanisms for the respective cells. Knockout mice for the CCR8 Th2 receptor showed deficient development in allergic airway responses. These mice had reduced eosinophillia and cytokine production. However, the bronchial hyperresponsiveness was not reduced. Interestingly, the correlation between theses results and deficient CCR8 remains to be determined (Berin, 2002).

Effector molecules

Many different inflammatory cells are involved in asthma, although the precise role of each cell type is not yet certain (Barnes, 1989; Barnes, 1992). It is evident that no single inflammatory cell is able to account for the pathophysiology of asthma, but some cells are predominant in asthmatic inflammation.

Mast cells

The mast cells have long been considered to be of paramount importance in the pathophysiology of asthma. It has been reported that there was striking increase in the number of mast cells in the bundle of smooth muscle (Brightling *et al.*, 2002) as well as increase in number of degranulated mast cells in patients with asthma (Carroll *et al.*, 2002). The mast cells are in the bone-marrow, enter the circulation as CD34+ mononuclear cells that are positive for stem cell factor and Fc-RI, travel to mucosal and submucosal sites in airway, and undergo tissue-specific maturation (Galli, 1997). Stem-cell factor is a chemoattractant for mast cells and is responsible for regulating their growth, function and survival. The receptor for stem-cell factor, c-kit, is expressed on the surface of the mast cells. It is also possible that stem cell factor is less readily metabolized in the airway of the persons with asthma or that there is a deficiency of a mediator that negatively regulates the release of stem-cell factor (Kassel *et al.*, 1999). There are at least two subpopulations of mast cells: mast cells with tryptase and mast cells with both tryptase and chymase. Although the role of these enzymes is not fully defined, inhibitors of tryptase have been shown to modulate the response of the airway to allergen (Clark *et al.*, 1995).

Mast cells also contain proteoglycans with diverse biologic properties or functions, ranging from being supporting structures for various proteins (i.e. remodeling) to exerting effects on the differentiation and proliferation of cells, the adhesion and motility of cells, and tissue morphogenesis. Mast cells produce several cytokines, including interleukin-1, interleukin-2, interleukin-3, interleukin-4, interleukin-5, granulocyte-macrophage colony stimulating factor, interferon-γ, and tumor necrosis factor α. The cross-linking of mast-cell-bound IgE by antigen through multiple Fc-RI on mast cells induces the activation of membrane and cytosolic pathways that cause the release of preformed mediators such as histamine and initiates the synthesis of arachidonic acid metabolites. The potential for the extracellular release of theses cytokines raises the possibility that mast cells contribute to both acute and chronic allergic inflammation (Table 1).

Eosinophils

Eosinophilic infiltration is a characteristic feature of asthmatic airway and differentiates asthma from other inflammatory conditions of the airway. Allergen inhalation results in a marked increase in eosinophils in bronchial mucosa which is a critical contributor to the late asthmatic reaction, and there is a close relationship between eosinophil counts in peripheral blood or bronchial lavage and airway hyperresponsiveness (Table 2).

Eosinophils were originally viewed as beneficial cells in asthma, as they have the capacity to inactivate histamine and leukotrienes, but is now seems more likely that they may play a damaging

Table 1. Mediators released by mast-cell (Serafin, 2001)

Class	Mediator	Effects
Preformed	Histamine	Vasodilation, vasopermiability, itch, cough, bronchoconstriction, rhinorrhea
	TNF-α	Adhesion molecule regulation
	Proteases	Vasodilation, vasopermeability, bronchoconstriction
	Heparin	Not known
Lipid derived	LTC_4	Bronchoconstriction, vasodilation, vasopermeability
	LTB_4	Leukocyte chemotaxis
	PGD_2	Vasodilation, vasopermeability, bronchoconstriction, mucus secretion
	PAF	Bronchoconstriction, leukocyte chemotaxis
Cytokine	TNF-α	Adhesion molecule regulation
	IL-1	Broad promotion of inflammation
	IL-2	Mast cell division
	IL-4	Mast cell division, B lymphocyte immunoglobulin class switching to produce IgE
	IL-5	Eosinophil differentiation and chemotaxis
	IL-6	Lymphocyte growth and differentiation
	IL-8	Leukocyte chemotaxis
	GM-CSF	Stimulate neutrophils, eosinophils and macrophages
	MIP-1α	Monocyte, T lymphocyte, eosinophil chemotaxis

Table 2. Role of eosinophil in the late asthmatic reaction

Eosinophil		
Class	Mediators	Effects
Crystalloid granule protein	Core- MBP Matrix-EPO, ECP	Respiratory epithelial desquamation, Cilliostasis M2 receptor dysfunction, ↓Mast cell and basophil degranulation Bronchial hyperresponsiveness
Lipid mediators	LTC_4, LTB_4, 5-HETE, PGE_1, PGE_2, TxB_2, PAF	Increased mucus secretion, Increased vascular permeability, Increased adhesion molecule expression, Stimulate smooth muscle cell proliferation, Bronchoconstriction, Eosinophil and neutrophil chemotaxis
Cytokines and Chemoknes	Autocrine-eosinophil active growth factors (IL-3, IL-5, GM-CSF), Immunoregulatory cytokines (IL-1, IL-2, IL-4, TGF-β, IFN-γ), Proinflamatory cytokines (IL-6, TNF-α, IL-16), Chemokines (IL-8, MIP-1α, RANTES)	Increased eosinophil survival, Increased adhesion molecule expression, Eosinophil and neutrophil chemotaxis, Sustained inflammation, Airway wall remodeling

role, and may be linked to the development of airway hyperresponsiveness through the release of basic proteins and oxygen-derived free radicals (Gleich, 1990). Eosinophilopoiesis begins in the bone marrow and is regulated by interleukin-3, interleukin-5 and granulocyte-macrophage colony stimulating factor. Inteleukin-5 has been shown to promote the growth and differentiation of airway eosinophils, in contrast to interleukin-3 and granulocyte-macrophage colony stimulating factor, acted as terminal eosinophil-differentiation factor. The mature eosinophil has dense intracellular granules that are sources of inflammatory proteins, including major basic proteins, eosinophil-derived neurotoxin, peroxidase, and cationic protein. Major basic protein, in particular, can directly damage airway epithelium, intensify bronchial responsiveness, and cause degranulation of basophils and mast

cells. These effects increase the severity of asthma. To participate in the allergic inflammatory response, the eosinophil must migrate from the circulation to the airway (Bochner, 1997; Wardlaw, 1999). Circulating eosinophils migrate to the airways by phenomenon of cell rolling, through interaction with P-selectin, and eventually adhere to the endothelium through the binding of integrins to adhesion proteins [vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1)]. As eosinophils enter the matrix of the membrane, their survival is prolonged by interleukin-5. On activation, eosinophils release inflammatory mediators such as leukotrienes and granule proteins to injure airway tissue (Corrigon, 1994).

Table 3. Individual role of Th2 cytokines in allergic airway inflammation

Effects of allergic airway responses	Th2 cytokines
Acute effects in the lung	
Airway eosinophilia	IL-4 IL-5
	IL-13
	(IL-4)
	(IL-9)
Mucus hypersecretion	IL-13
	(IL-9)
Airway hyperresponsiveness	IL-13
Airway remodeling/pro-fibrotic effects	IL-4
General effects on Th2 type responses	IL-13
Th2 cell differentiation	
IgE isotype class switching	IL-4
	(IL-13)
	(IL-13)

Kung *et al.*, 1995; Van Oostarhout *et al.*, 1995; Hoster *et al.*, 1996; Lee *et al.*, 1997.

Lymphocytes

Mucosal-biopsy specimens obtained from patients during an episode of asthma after the inhalation of allergen contain lymphocytes, many of which express surface markers of activation (Azzawi *et al.*, 1990). T-lymphocytes play a very important role in coordinating the inflammatory response in asthma through the release of specific patterns of cytokines, resulting in the recruitment and survival of eosinophils and in the maintenance of mast cells in the airway. There are two types of T-lymphocytes: helper CD4+ T cells and killer CD8+ T cells. In simple terms, type 1 helper T (Th1) cells produce interleukin-2 and interferon-γ, which are essential for cellular defense mechanisms. In contrast, type 2 helper T (Th2) cells produce cytokines (IL-4, IL-5, IL-6, IL-9 and IL-13) that mediate allergic inflammation. Furthermore, there is reciprocal inhibition, in that Th1-type cytokines inhibit the production of Th2-type cytokines and vice versa. CD8+ T cells may be classified in a similar fashion according to their cytokine profiles (Tc1 and Tc2) (Sad *et al.*, 1995). It is hypothesized that allergic asthmatic inflammation result from a Th2-mediated mechanism. A number of observations support this hypothesis. Recently, high concentrations of mRNA for GATA-3, a transcription factor that is confined to Th2 cells, were found in bronchial-biopsy specimens from patients with asthma (Nakamura *et al.*, 1999). It seems that the bronchial mucosa in patients with asthma contains an excess of activated Th2 cells irrespective of the allergic sensitization of the patient. The idea that allergic inflammation in allergic asthma arises from an imbalance between Th1 and Th2 cells focused an attention on the Th1-type cytokine interferon-γ. Since, interferon-γ inhibits the synthesis of IgE and the differentiation of precursor cells to Th2 cells, a lack of interferon-γ would induce the Th2-type cytokine pathway to promote allergic inflammation (Table 3). The evidence from *in vivo* studies of asthma, however, conflicts with this hypothesis.

An imbalance between Th1 and Th2 cells and the origin of asthma

Although we question the importance of an imbalance between Th1 cells and Th2 cells in patient with established asthma, the possibility that this imbalance contribute to the cause and evaluation of atopic diseases, including asthma. Largely, as a result of Th2-trophic factors from the

placenta, the population of T cells in the cord blood of newborn infants is skewed toward a Th2 phenotype (Prescott *et al.*, 1998). The extent of imbalance between Th1 and Th2 cells (as indicated by diminished production of interferon-γ) during the neonatal phase may be useful in predicting the subsequent development of allergic disease, asthma, or both (Tang *et al.,* 1994; Halonen and Martnez, 1997; Prescott *et al.,* 1998). To reduce the risk of asthma and allergy in childhood, some have suggested that infants at high risk for these conditions should be exposed to stimuli that up-regulate Th1-mediated responses, so as to restore imbalance during a critical time in the development of the immune system and the lung.

The hygiene hypothesis has been articulated as a means to explain the increasing prevalence of asthma in industrialized western countries than in less technologically advanced societies (Larsen, 1992; Margan and Martinez, 1992). According to the hygiene hypothesis, early airway infections and higher levels of exposures to animal allergens like farm animals, cat, dog etc. affects the relative balance of Th1 versus Th2 airway immunological profile. Here, early exposure to the various triggers that may occur with higher frequency in a rural area may tilt this balance to a Th1 paradigm and hence be protected against the allergic diathesis that is characteristic of a Th2 paradigm. In cleaned urban westernized lifestyle, such early childhood exposure is lacking, and the paradigm therefore shifts closer to the allergic diathesis of Th2, which results in a higher incidence of asthma and other allergic diseases (Fig. 2) (Weiss, 2002). Endotoxins are inflammatory lipopolysaccharide (LPS) molecules from Gram negative bacteria that are ubiquitous in the indoor environment (Thorne and Heederik, 1999). Inhaled Endotoxins trigger cellular activation and cytokine release from macrophages and other myeloid cells through LPS binding protein and CD14-dependant delivery of monomeric Endotoxins to cells expressing MD-2 and TLR4 on their surface. Theses responses to inhaled endotoxins can exacerbate classical features of asthma like airflow obstruction and airway inflammation, airway hyperreactivity, and airway remodeling (Tobias *et al.*, 1999; Gioannine *et al.*, 2003).

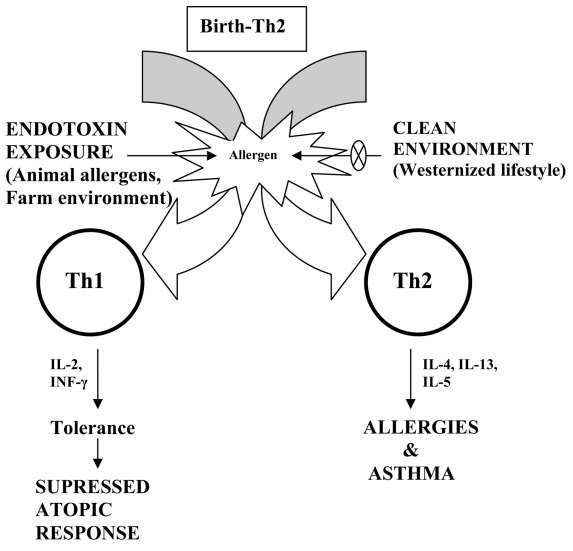

Fig. 2. Hygiene hypothesis and asthma.

Alveolar macrophages

Macrophages are derived from blood monocytes and the primary function of alveolar macrophages in the normal airway is to serve as 'scavengers', engulfing and digesting bacteria and foreign materials. Macrophages may traffic into airways in asthma and may be activated by allergen via low affinity IgE receptors (Lee and Lane, 1992). A number of mediators produced and released by macrophages like platelet-activating factor, leukotriene-B_4, leukotriene-C_4 and leukotriene-D_4 which play a role in initiating and amplifying inflammation in allergic asthma. Additionally, alveolar macrophages are able to produce neutrophil chemotactic factor and eosinophil chemotactic factor, which in tern further the inflammatory process. Alveolar macrophages normally have suppressive effect on lymphocyte function, but this may be impaired in asthma after allergen exposure (Spiteri *et al.*, 1994).

Neutrophils

The role of neutrophils in human asthma is less clear. However, high numbers of neutrophils have been reported to be present in the airway of patients who died from sudden-onset fatal asthma (Stempel and Szefler, 1992). This suggests that neutrophils play a pivotal role in disease process, especially in acute exacerbation of asthma and in some patients with long-lasting or corticosteroid-dependent asthma. The neutrophils also can be a source for a variety of mediators, including platelet-activating factor, prostaglandins, thromboxanes, and leukotrienes, that contribute to BHR and airway inflammation.

Fibroblasts and myofibroblasts

Fibroblasts are found frequently in connective tissue. Human lung fibroblasts may behave as inflammatory cells on activation by interleukin-4 and intrleukin-13.the myofibroblasts may contribute to the regulation of inflammation via the release of cytokines and to tissue remodeling. In asthma, myofibroblasts are increase in numbers beneath the reticular membrane, and there is an association between their numbers and thickness of reticular basement membrane.

Epithelial cells

Activation of airway epithelial cells of innate and adoptive immune system (like alveolar macrophage, neutrophil, eosinophil, dendritic cell, mast cell, natural killer cell and lymphocytes) may be documented in development of asthma. Epithelial cells also produce inflammatory mediators, such as endothelins, proinflammatory cytokines, chemokines and growth factors (Devalia and Davies, 1993). Epithelial cells may play a key role in translating inhaled environmental signals into an airway inflammatory response and are probably the main target cell for inhaled glucocorticoids (Pieter and Robert, 2004).

The above mentioned effector ligands up regulate a distinct set of transcription factors. In particular, there are two transcription factors that have a predominant role in asthma hypersensitivity reactions. One of these transcription factors is Stat-6 and is involved in the signal transduction pathway affected by interleukin-4, interleukin-5 and interleukin-13. It is believed that IL-4 and IL-13 Are necessary to induce Stat-6, and in turn Stat-6 activates genes responsible for bronchial hyperresonsiveness and allergic inflammation. Stat-6 is also vital for the development of CD4+ Th2 cells and Stat-6 null mutants fail to induce asthma due to lack of IL-5 production. Adoptive transfer of Stat-6 +/+ T cells into Stat-6 null mutants also demonstrated that Stat-6 is essential for eosinophilia mucus production. The second important transcription factor in allergic asthma is GATA 3, which is involved in Th0 to Th2 differentiation and induced in the asthmatic airways (Berin, 2002). Besides these two, a transcription factor that play a critical role in asthma is nuclear factor-kappa B (NF-κB) which can be activated by multiple stimuli, including protein kinase C activators, oxidants and proinflammatory cytokines (such as IL-1β and TNF-α). NF-κB is predominant transcription regulating the expression of iNOS, COX-2, chemokines (IL-8, RANTES, MIP-1α), proinflammatory cytokines (TNF-α, GM-CSF) and adhesion molecules (ICAM-1, VCAM-1) (Siebenlist *et al.*, 1994). NF-κB in epithelial cells may play a pivotal role in amplifying inflammation in asthma (Barnes and Karin, 1996). This is further supported by studies showing that NF-κB is potentially inhibited by glucocorticoids (Barnes and Adcock, 1993).

Costimulatory molecules

Several costimulatory factors are believed to play a crucial role in the development of tolerance and immunity. One set of costimulatory molecules is OX40 and OX40L, members of tumor necrosis factor family of receptors. In null mutant mice for OX40, large numbers of recruited eosinophils, IgE production and concentration of Th2 cytokines in

the serum and bronchoalveolar lavage were dependent upon the presence of OX40. Moreover, globlet cell hyperplasia, mucus production, and airway hyperresponsiveness (AHR) were suppressed in the absence of OX40 which illustrating the importance of OX40 in Th2 asthma responses. Another important costimulatory set of molecules is ICOS and ICOSL (ICOS is expressed on T cells and ICOSL is expressed on dendritic cells). Its importance in the immune response is highlighted by the fact that blocking ICOS-ICOSL interactions inhibits respiratory tolerance and suppressed regulatory T cells development. Inhibition of ICOS during initial stimulation and naïve T cells results in the production of more Th1 cells suggesting smaller concentration of Th2 developmental cytokines. Murine models deficient in ICOS have decreased IgE production, Th2 cytokines, and AHR. ICOS null mutation in murine model suppress IL-4 and IL-13 production but make the mice susceptible to inflammatory lung disease by airway challenge in primed mice (Akbari *et al.*, 2003).

Adhesion molecules

An important step in the inflammatory process is the adhesion of the various cells to each other and the tissue matrix to facilitate infiltration and migration of these cells to the site of inflammation (Bethesda, 1991). The adhesion molecules thought to be important in inflammation include the integrins, immunoglobulin supergene family, selectins, and carbohydrate ligands including ICAM-1 and VCAM-1 (Corrigon, 1994). In allergic inflammatory response, eosinophil migration occurs through the phenomenon of cell rolling, which is mediated by P-selectin on the surface of eosinophils. Cell rolling activates eosinophils and requires the participation of the β_1 and β_2 classes of integrins on the eosinophil surface. Eosinophils and lymphocytes express the β_1 integrin $\alpha_4\beta_1$ integrin (also referred as very late antigen 4, or VLA4), which binds to its ligand, vascular-cell adhesion molecule 1. Adhesion of the eosinophil to vascular-cell adhesion molecule 1 decreases the threshold for activation of cell by mediators (Nagata *et al.*, 1995). The interactions between the β_2 integrins on eosinophils and intracellular-cell adhesion molecule 1 on vascular tissue appear to be important for the transendothelial migration of eosinophils (Yamamoto *et al.*, 1998). VCAM-1 appears to be more selective for eosinophils (Pilewski and Albelda, 1995). The β_1 and β_2 intigrins are consecutively expressed on the surface of eosinophils but their state of activity is regulated by a variety of cytokines and chemokines. The chemokines RANTES, macrophage inflammatory protein 1α, and the eotaxins are central to the delivery of eosinophils to the airway (Luster, 1998; Nickel *et al.*, 1999; Hamid and Minshall, 2000). Chemokines have been detected on cells and in airway tissue from patients with asthma. Berkman *et al.* (1996) found that the constitutive expression of messenger RNA (mRNA) for RANTES was greater in the airway of patients with asthma than in normal subjects. *Holgate et al.* (1997) detected RANTES, macrophage inflammatory protein 1α, and monocyte chemotactic protein 1 in the airway of normal subjects and patients with asthma within four hours after airway challenge with allergen. At 4 h, there was a positive correlation between RANTES concentrations and the number of eosinophils in the air space, and the concentration of all three chemokines returned to base-line values within 24 h. Ying *et al.* (1997) performed immunohistochemical studies of airway-biopsy specimens from normal subjects, allergic patients with asthma, and patients with nonallergic asthma and found that epithelial cells, endothelial cells, and macrophages were the primary sources of eotaxin, eotaxin-2, RANTES, and monocyte chemotactic protein 3 and 4. Moreover, significant correlations were found between the degree of staining of eosinophils for EG2, a monoclonal antibody against the cleaved form of eosinophil cationic protein, and the concentration of eotaxin.

Collectively, the characteristics of many of the chemokines that act through the CCR3 receptor on the eosinophil, such as eotaxin, suggest that they are important in attracting eosinophils to the airway in asthma.

Inflammatory mediators

Many different mediators have been implicated in asthma and they may have a variety of effects on the airways which could account for the pathological features of asthma (Barnes *et al*., 1988). Mediators such as histamine, prostaglandins and leukotrienes contract airway smooth muscle, increase microvascular leakage, increase airway mucus secretion and attract other inflammatory cells. Because each mediator has many effects, the role of individual mediators in the pathophysiology of asthma is yet not clear.

Associated with asthma for many years, histamine is capable of inducing smooth muscle contraction and bronchospasm and is thought to play a role in mucosal edema and mucus secretion (Bethesda, 1991). Lung mast cells are important source of histamine. The release of histamine can be stimulated by exposure of airways to variety of factors including physical stimuli and relevant allergens (Bethesda, 1991; Hill *et al*., 1992).

Besides histamine release, arachidonic acid and its metabolites (i.e. prostaglandins, leukotrienes, and platelet-activating factor) play a crucial role. Once arachidonic acid is released, it can be broken down by enzyme cyclooxygenase to form the prostaglandins. A further breakdown product, prostaglandin D_2, is potent bronchoconstricting agent. It is unlikely that prostaglandin D_2 can produce sustained effects on airway or inflammation; however, its role in asthma remains to be determined. Similarly, prostaglandin $F_{2\alpha}$ is a potent bronchoconstrictor in patients with asthma and can enhance the effect of histamine (Bethesda, 1991). However, its pathophysiologic role in asthma is unclear. Another cyclooxygenase product, prostaglandin I_2 (prostacyclin) is known to be produced in lung. It is unclear whether prostaglandin I_2 is important as a bronchoconstricting agent in human; however, it may contribute to inflammation and edema owing to its effects as a vasodilator.

The 5-lipoxygenase pathway of arachidonic acid breakdown is responsible for production of the class of compounds called *cesteinyl leukotrienes* (LTs). LTC_4, LTD_4 and LTE_4 constitute the slow-reacting substance of anaphylaxis (SRS-A). They are potent constrictors of human airway and have been reported to increase AHR and may play an important role in asthma (Arm and Lee, 1993). These leucotrienes are liberated during inflammatory processes in the lung. LTD_4 and LTE_4 share a common receptor (LTD_4 receptor) that, when stimulated, produces bronchospasm, mucus secretion, microvascular permeability, and airway edema. Potent LTD_4 antagonists protect (by about 50%) against exercise- and allergen-induced bronchoconstriction (Manning *et al*., 1990; Taylor *et al*., 1991). Chronic treatment with leukotriene antagonists improve lung function and symptoms in asthmatic patients, although the degree of improvement is modest compared with inhaled glucocorticoids (Spector *et al*., 1994). The role of leukotrienes in chronic asthma remains to be defined and several clinical trials with potent leukotriene antagonists are currently underway.

A mediator which has attracted considerable attention recently is platelet-activating factor (PAF), since it mimics many of the features of asthma, including AHR (Barnes *et al*., 1988). PAF is thought to be produced by macrophages, eosinophils, and neutrophils within the lung and involved in the mediation of bronchospasm, sustained induction of BHR, edema formation, and chemotaxis of eosinophils. Initial results with potent PAF antagonists such as apafant (WEB 2086) and modipafant in chronic asthma have been disappointing in clinical trials of asthma (Spence *et al*., 1994; Kuitert *et al*., 1995).

Thromboxane A_2 is produced by alveolar macrophages, fibroblasts, epithelial cells, neutrophils,

and platelets within the lung (Martin, 1993). Indirect evidence from animal models suggest that Thromboxane A_2 may have several effects, including bronchoconstriction, involvement in the late asthmatic response, and involvement in the development of airway inflammation and BHR. Potent and specific Thromboxane synthase inhibitors will be crucial tools for understanding the role of thromboxanes in asthma.

Cytokines are increasingly recognized to be important in chronic inflammation and play a critical role in orchestrating the type of inflammatory response. Many inflammatory cells (macrophages, mast cells, eosinophils, and lymphocytes) as well as structural cells such as epithelial cells and endothelial cells are capable of synthesizing and releasing variety of cytokines and may therefore participate in the chronic inflammatory response (Barnes, 1994). Research in this area is hampered by a lack of specific antagonists, although important observations have been made using specific neutralizing antibodies. The cytokines which appear to be of particular importance in asthma include the lymphokines secreted by T-lymphocytes: IL-3, IL-4, IL-5, IL-1, IL-6, TNF-α, GM-CSF, interferon-γ etc. IL-3 is important for the survival of mast cells in tissues. The main role of IL-4 in allergic airway inflammation is during the initial priming of Th2-effector cells. In IL-4-defficient mice, defective priming of Th2 cells in the absence of IL-4 resulted in failure to generate allergic inflammatory responses after subsequent airway challenge (Oony *et al.*, 1996). IL-4 is critical in switching B-lymphocytes to produce IgE and for expression of VCAM-1 on endothelial cells.IL-5 which is of critical importance in the differentiation, survival and priming of eosinophils. Direct administration of IL-5 to the airway of humans causes mucosal eosinophilia and an increase in bronchial responsiveness (Shi *et al.*, 1998). Challenge of the airway with allergen increases the local concentration of IL-5, which correlates with the degree of airway eosinophilia (Sedgwick *et al.*, 1991). In mice lacking the gene for IL-5, eosinophilia does not occur after challenge by an antigen (Foster *et al.*, 1996). There is evidence for increasing the gene expression of IL-5 in lymphocytes in bronchial biopsies of patients with symptomatic asthma (Hamid *et al.*, 1991). IL-5 is the predominant eosinophil-active cytokine present in bronchoalveolar lavage (BAL) fluid during allergen induced late phase inflammation (Kita *et al.*, 1993). Other cytokines, such as IL-1, IL-6, TNF-α and GM-CSF may be important in amplifying the inflammatory response. TNF-α may be important amplifying mediator in asthma and is produced in increased amounts in asthmatic airways. Inhalation of TNF-α causes increased airway responsiveness in normal individuals (Thomas *et al.*, 1995). Interferon-γ increases not only expression of CD69, HLA-DR, and intercellular adhesion molecule 1 (all of which are markers of cell activation) on eosinophils but also viability of eosinophils (Hartnell *et al.*, 1993). These and other data (Holtzman *et al.*, 1996; Randolph *et al.*, 1999) suggest that interferon-γ contributes the activation of eosinophils and thus is likely to augment inflammation.

Endothelins are potent peptide mediators that are potent vasoconstrictors and brnchoconstrictors (Bernes, 1994). They also induce airway smooth muscle cell proliferation and fibrosis and therefore play a role in chronic inflammation of asthma. There is evidence for increased expression of endothelins in asthma, particularly in airway epithelial cells (Springall, 1991).

Nitric oxide (NO) is produced by several cells in the airway by NO synthases (NOS) (Bernes PJ, 1995). An iducible form of the enzyme (iNOS) is expressed in epithelial cells of asthmatic patients (Hamid *et al.*, 1993) and can be induced by proinflammatory cytokines in airway epithelial cells (Robbins *et al.*, 1994). This may account for the increased concentration of NO in exhaled air of asthmatic patients (Kharitonov *et al.*, 1994) and recent investigations measuring exhaled NO concentration have suggested that it may be a

useful measure of ongoing lower airways inflammation in patient with asthma as well as for measuring effectiveness of therapy (Drummond *et al.*, 1994). NO itself is a potent vasodilator and this may increase plasma exudation in the airways; it may also amplify the Th2-lymphocyte mediated response (Barnes and Liew, 1995).

In our final conclusion, immunity is our friend in normal conditions but when there is a talk of autoimmune disease like asthma, there is no great foe other than immunity. So, to get victory on asthma, we have to bit our foe that is immunity.

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