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# Immunobiology of Asthma

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## Key Words

pathology, cytokines, chemokines, remodeling, immunology

## Abstract

Asthma is characterized by chronic inflammation of the airways in which there is an overabundance of eosinophils, mast cells, and activated T helper lymphocytes. These inflammatory cells release mediators that then trigger bronchoconstriction, mucus secretion, and remodeling. The inflammatory mediators that drive this process include cytokines, chemokines, growth factors, lipid mediators, immunoglobulins, and histamine. The inflammation in allergic asthma can be difficult to control. This is mainly due to the development of an adaptive immunity to an allergen, leading to immunological memory. This leads to recall reactions to the allergen, causing persistent inflammation and damage to the airways. Generally, in asthma inflammation is directed by Th2 cytokines, which can act by positive feedback mechanisms to promote the production of more inflammatory mediators including other cytokines and chemokines. This review discusses the role of cytokines and chemokines in the immunobiology of asthma and attempts to relate their expression to morphological and functional abnormalities in the lungs of asthmatic subjects. We also discuss new concepts in asthma immunology, in particular the role of cytokines in airway remodeling and the interaction between cytokines and infection.

## INTRODUCTION

Histopathological changes in the bronchial and bronchiolar walls in asthma involve the mucosa (i.e., the epithelium and lamina propria), submucosa [with included airway smooth muscle (ASM) and mucus-secreting glands], and adventitia (the interface between airway and surrounding lung parenchyma) (1, 2). Information on the pathological changes in asthma has been obtained from studying airway sections from asthma deaths; patients who had asthma but who died from non-asthma-related causes; surgically resected lung; and endoscopic biopsies of mild, moderate, and severe asthmatic subjects. Tissue from transbronchial biopsies of severe asthmatics has also been studied for inflammation and remodeling

It is now accepted that asthma is a chronic inflammatory condition, and evidence of inflammation can be observed in mild, moderate, and severe disease. However, the relative magnitude, type of inflammatory cells, and site of the inflammatory infiltrate may differ among patients. Many cells are involved in the immune and inflammatory responses to allergens in asthma; these include T cells, eosinophils, mast cells, and neutrophils.

The role of the activated T lymphocyte in controlling and perpetuating chronic inflammation in asthma has received much attention (3). In some studies, T cell activation can be related to measures of asthma severity, such as the degree of airway narrowing or airway hyperresponsiveness (AHR), as well as the bronchial eosinophil response (4). The association between tissue eosinophilia and asthma is strong, but the degree of tissue eosinophilia varies with each case and with the duration of the terminal episode (5, 6).

Mast cells are usually found adjacent to blood vessels in the lamina propria in normal human airways, but in asthma they are observed in the airway epithelium (7), the airway mucous glands, and the ASM (8–10). Neutrophilic inflammation is found in severe persistent asthma (11), asthma exacerbations (12–14), sudden-onset fatal asthma (15), occupational asthma (16), nocturnal asthma (17), and even childhood asthma (18). Neutrophils may play a role in the pathophysiology of airway disease through their release of reactive oxygen species, cytokines, lipid mediators, and enzymes including elastase, cathepsin G, myeloperoxidases, and nonenzymatic defensins (19).

Dendritic cells and their subtypes are key antigen-presenting cells that respond rapidly to antigenic challenge with kinetics similar to those of neutrophils (20). They form an interface between innate and adaptive immunity and orchestrate both primary and secondary immune responses (21). They are present throughout the respiratory tree and number approximately 500 cells per $mm^2$ within the epithelium (22). Inflammatory cells and immune responses are regulated by a number of immune mediators that are secreted from inflammatory and structural cells. In this review, we focus on cytokines and chemokines and their possible role in the immunobiology of asthma.

## CYTOKINES AND CHEMOKINES

Cytokines are a family of small glycosylated proteins that are involved in cell-to-cell signaling, cellular growth, differentiation, proliferation, chemotaxis, immunomodulation, immunoglobulin isotype switching, and apoptosis. The actions of cytokines are mediated through specific cytokine receptors on the surfaces of target cells. Although cytokines usually have effects on adjacent cells, they can act at a distance and can have effects on the cells producing the cytokines themselves. Many of these cytokines exhibit pleiotropy and have overlapping functions, making their individual roles in the pathogenesis of asthma and allergic disease difficult to differentiate.

Until recently, T lymphocytes and eosinophils were considered to be the major source of cytokines in asthma (**Figure 1**), but researchers now recognize that cytokines are produced not only by other inflammatory cells, but also by structural cells including epithelial, endothelial and ASM cells, and fibroblasts. To

date, more than 30 different cytokines involved in asthma pathology have been identified, and this number continues to grow. Among these cytokines are T cell–derived molecules such as the so-called T helper–1 (Th1) cells [interleukin (IL)-2, interferon (IFN)-γ, and IL-12], Th2 cells (IL-4, -5, -9, -13, and -25), Th3 or T regulatory cytokines [IL-10 and transforming growth factor beta (TGF-β)], and Th-17 cells (IL-17A and -17F), all of which are involved in the regulation of cell-mediated and humoral immunities. Although the distinction between Th1 and Th2 cells in humans is not as clear as in mice, there is overwhelming evidence in the literature supporting the notion that allergic inflammation is driven by an imbalance between Th1 and Th2 cytokines, favoring the Th2 arm of the immune response (**Figure 2**). Recently, Th-17-associated cytokines were also implicated in asthma immunobiology (W. Ramli, J. Martin & Q. Hamid, unpublished data). Other cytokines include proinflammatory cytokines [IL-1β, -6, and -11; tumor necrosis factor (TNF)-α; and granulocyte/macrophage colony–stimulating factor (GM-CSF)] that are involved in innate host defense, anti-inflammatory cytokines (IL-10, IFN-γ, IL-12, and IL-18), growth factors [platelet-derived growth factor (PDGF), TGF-β, fibroblast growth factor (FGF), and epidermal growth factor (EGF)], and chemotactic cytokines or chemokines [RANTES, monocyte chemoattractant protein (MCP)-1–MCP-5, eotaxin, and IL-8]. In this review, which focuses on the role of cytokines and chemokines in asthma, cytokines and chemokines are broadly categorized on the basis of their functional activities and are subdivided into (*a*) eosinophil-associated cytokines, (*b*) immunoglobin E (IgE)-mediated cytokines, (*c*) remodeling-associated cytokines, and (*d*) immunomodulatory cytokines.

## IMMUNOGLOBIN E–ASSOCIATED CYTOKINES

Asthma is clinically categorized into occupational, nonatopic, and atopic (allergic) forms; the vast majority of asthmatics have the atopic form. A central mediator in atopic asthma is the IgE antibody, which is produced by sensitized allergen-specific B cells (**Figure 2**). Allergens are antigens that can (*a*) elicit hypersensitivity or allergic reactions and (*b*) increase IgE levels in the serum in susceptible subjects subsequent to stimulation. By presenting the allergen fragments in conjunction with the major histocompatibility complex (MHC), B cells can activate specific Th2 cells to produce numerous cytokines, leading to further B cell activation and antibody release. IgE antibodies bind to the high-affinity IgE receptor Fc epsilon receptor I (FcεRI) that is present on mast cells, eosinophils, and basophils, thereby sensitizing these cells to antigen exposure. Subsequently, cross-linking of adjacent IgE–FcεRI complexes by allergens triggers (*a*) the degranulation of cytoplasmic vesicles containing histamine and (*b*) the de novo formation of eicosanoids and reactive oxygen species. This results in smooth muscle contraction, mucous secretion, and vasodilatation, all of which are hallmarks of asthma. IgE-producing B cells play a critical role in allergic inflammation; consequently, factors responsible for their activation—namely IgE-associated cytokines such as IL-4, IL-9, and IL-13—are of considerable interest.

IL-4 is vital for the regulation of growth, differentiation, activation, and function of B cells

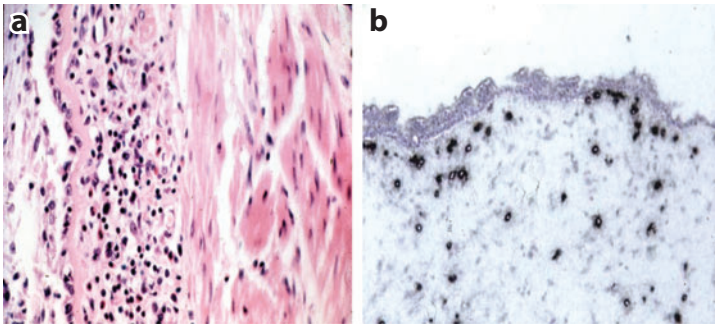


**Figure 1**

T cells are the predominant cells that infiltrate the airways in asthma and are the major source of cytokines. (*a*) A hematoxylin- and eosin-stained section showing T cell infiltration. (*b*) An in situ hybridization of section from a bronchial biopsy from a patient with asthma showing messenger RNA expression of interleukin-4 in T cells.

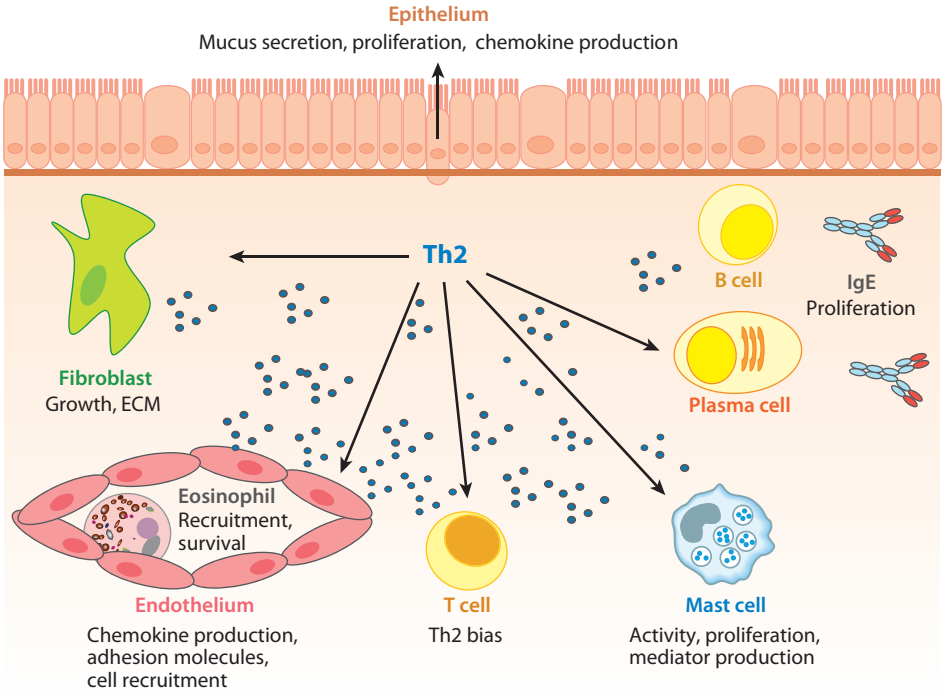


**Figure 2**

The possible effect of T helper–2 (Th2) cytokines on various cells in the lung and the cytokines' potential role in asthma. Abbreviations: ECM, extracellular matrix; IgE, immunoglobin E.

(23) (**Figure 2**). IL-4 exerts its actions by a specific cell-surface receptor composed of the IL-4Rα chain and the γ common chain. IL-4 increases expression of the antigen-presenting proteins, MHC class II molecules, on B cells, resulting in increased allergen-presentation capacity to Th2 cells (24). On the vasculature, IL-4 promotes expression of VCAM-1 on endothelium, thereby allowing for recruitment of eosinophils and other inflammatory cells such as T cells, monocytes, and basophils from the blood into the sites of inflammation (25). IL-4 also induces isotype switching, a process that leads to the production of IgE by B cells. After switching occurs, IL-4 potentiates IgE production. Furthermore, IL-4 enhances the IgE-mediated response by upregulating IgE receptors on inflammatory cells within the airway (26). Conversely, activation of IgE by IL-4 can be diminished by cross-regulation from Th1 cytokines (**Figure 1**). IFN-γ, a Th1 cytokine, can suppress isotype switch recombination to the IgE isotype in B cells activated by IL-4 (27). Additionally, IFN-γ also inhibits IL-4-induced expression of the low-affinity IgE receptor (28). IL-4Rα-deficient mice are more resistant to the development of features of asthma than are the IL-4-deficient mice (29). However, the latter mice still develop AHR, which suggests that there exist other cytokines that can initiate signal transduction via the IL-4 receptor.

IL-13 has a 70% sequence homology with IL-4, and it binds a heterodimer composed of the IL-4Rα chain and an IL-13Rα chain (30). Like IL-4, IL-13 is produced by Th2 cells and is found in high concentrations within allergic tissues (31, 32). Owing to the redundancy in IL-4Rα binding, IL-4 and IL-13 exhibit some degree of functional overlap. Similarly to IL-4, overexpression of IL-13 within the lungs results in IgE production, inflammation, mucus hypersecretion, eosinophilia, and upregulation

of VCAM-1. However, the unique nature of IL-13 can be observed in its effects on airway sensitivity to contractile agonists, whereby the blocking of IL-13 prevents AHR in mice following antigen challenge (33). Accordingly, researchers hypothesize that IL-13 is the primary factor involved in the expression and induction of allergen-induced AHR.

Both IL-4 and IL-13 are critical in the induction and regulation of allergic asthma through their production of IgE. Interestingly, the effect of exogenous IL-13 depends on when it is given in relationship to allergen exposure: Its administration after initial allergen sensitization in mice has no effect on serum IgE levels (33). The emerging paradigm is that IL-13 induces features of the allergic response via its actions on epithelial and smooth muscle cells rather than through traditional effector pathways involving eosinophils and IgE-mediated events (34).

IL-9 is also relevant to IgE-dependent host responses. IL-9 is a Th2 cytokine, and its expression is regulated by a variety of mediators, in particular IL-2, which stimulates its production. Although IL-9 is produced by a variety of cell types including mast cells, eosinophils, and neutrophils, the major sources of this cytokine are Th lymphocytes. Transgenic mice overexpressing IL-9 have increased serum levels of all Ig isotypes, including IgE, and an associated accumulation of B cells in the lungs (35, 36). In vitro, IL-9 enhances IL-4-mediated IgE production by both human and murine B cells (37). IL-9 also stimulates protease production from mast cells and induces their expression of FcεRI. This suggests that in addition to potentiating IgE production, IL-9 primes mast cells to respond to allergen challenge through increased cell-surface expression of FcεRI and the production of proinflammatory mediators.

In addition to influencing IgE-mediated immunity, IL-9 can coordinate a multitude of responses associated with asthma through direct, indirect, and synergistic actions. IL-9 has been identified as a T cell growth factor and is capable of stimulating the proliferation of activated T cells (38–40). IL-9-transgenic mice demonstrate in vivo increased AHR, marked eosinophilia, mucous overproduction (41), and increased expression of eotaxin and MCP-1, -3, and -5 in airway epithelial cells (42).

The newly described cytokine IL-25 (also known as IL-17E) also seems to play a role in the regulation of IgE-mediated responses. IL-25 stimulates IgE synthesis and eosinophilia in mice models of allergic inflammation by stimulating the release of IL-4 and IL-5 cytokines (43). As the roles of novel cytokines such as IL-25 are clarified, especially with regard to the regulation of IgE-mediated inflammation, it becomes evident that the cytokine network regulating inflammation is broad and complex. Nonetheless, insofar as they prove to be critical mediators of the inflammatory process, the stimulatory effects of these cytokines make them obvious targets in the treatment of allergic diseases **(Figure 3)**.

## EOSINOPHIL-ASSOCIATED CYTOKINES

Eosinophils are prominent in allergic airway disease and are still considered by many to be the hallmark of asthma. Increased numbers of eosinophils in the bronchial mucosa as well as in the bronchoalveolar lavage (BAL) and sputum are consistent features of asthma, and BAL eosinophilia has been linked to development of the late airway response and asthma severity. Increased eosinophilia in asthmatics is observed not only in the large or the central airways of these patients but also in the peripheral parts of the lungs (44). Although terminal differentiation of eosinophils occurs within the bone marrow, recent evidence indicates that eosinophils can also differentiate locally at the site of inflammation and that the presence of eosinophils within allergic mucosal tissue is not solely due to infiltration of mature cells (45).

Teleologically, eosinophils form part of the host defense against parasitic infestation. The biological activity exerted by these cells is largely attributable to their release of prestored granular proteins, including eosinophil cationic protein, eosinophil peroxidase, and major basic

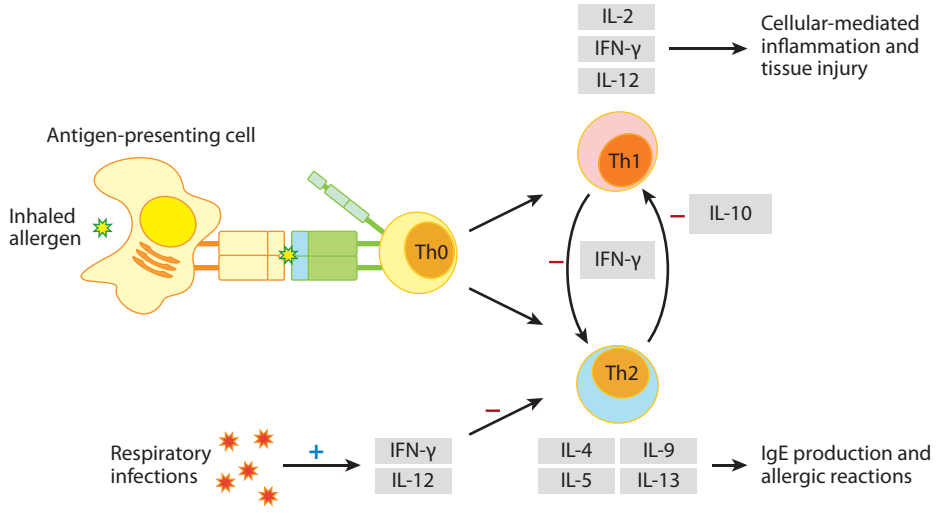


**Figure 3**

The regulation of T cells, cytokines, and factors that may bias cytokines' gene expression toward T helper–1 (Th1) or Th2 patterns. Abbreviations: IFN, interferon; IgE, immunoglobin E; IL, interleukin.

protein. These potent cytotoxic proteins have been found in high concentrations in the sputum of asthmatic patients and are thought to play an important role in the epithelial damage observed in asthmatic patients. In addition to cytotoxic proteins, eosinophils can synthesize and release oxygen radicals and lipid mediators (e.g., $LTB_4$, $LTC_4$, and PAF), as well as numerous cytokines (e.g., IL-1, -2, -3, -4, -5, -6, -10, -12, and -13; TNF-$\alpha$; and GM-CSF) and chemokines (e.g., IL-8, RANTES, and MIP-1$\alpha$). Recently, it was suggested that eosinophils may play a role in airway remodeling because they have the ability to synthesize and release fibrogenic cytokines including TGF-$\beta$, IL-11, IL-17, and IL-25 (46). Together, these eosinophil-associated cytokines are responsible for the tissue-destructive potency of this proinflammatory cell.

IL-5 is the most important Th2 cytokine associated with eosinophils, and it can regulate most aspects of eosinophil behavior including eosinophil growth, maturation, differentiation, survival, and activation (**Figure 2**). Although IL-5 is produced by T helper cells, cytotoxic T lymphocytes, and mast cells, eosinophils are the predominant sources of this cytokine. Human eosinophils express IL-5 messenger RNA (mRNA) and release IL-5 protein in vitro. Allergen challenge in the bronchial segments results in increased IL-5 mRNA expression in eosinophils in BAL fluid, with a 300-fold increase in IL-5 protein concentrations (47). IL-5 plays a central role in accumulation and activation of eosinophils in the lungs, an effect readily seen in IL-5-overexpressing transgenic mice that have lifelong eosinophilia (48). Moreover, IL-5 is a potent eosinophil chemoattractant (3), and it upregulates integrin receptor expression on eosinophils, thereby promoting adherence of eosinophils to VCAM-expressing endothelial cells and eosinophil accumulation.

Studies with IL-5 monoclonal antibodies in animal models of allergic inflammation clearly support a role for IL-5 in allergic disease; however, similar studies in humans have been disappointing. Although blocking IL-5 was effective in abolishing blood and sputum eosinophilia, it did not protect against the allergen-induced late airway response, nor did it have any effect on baseline AHR in mild asthmatics (49). These results question the role of eosinophils in airway responsiveness in humans and suggest that alternate mechanisms and/or factors are

responsible for airway narrowing in asthmatic patients.

Although secondary in importance to IL-5, IL-3 and GM-CSF are also typically viewed as eosinophil-associated cytokines. IL-3 and GM-CSF are pluripotent hematopoietic growth factors that stimulate the formation of not only eosinophil lineages but also neutrophil, erythroid, and monocytic lineages. Increased expression of GM-CSF has been documented in the bronchial epithelium and in the eosinophils of asthmatics following endobronchial allergen challenge. GM-CSF is involved in the priming of eosinophils and accounts for increased eosinophil survival in the BAL fluid of asthmatic patients. In addition, GM-CSF may also be involved in development of chronic eosinophilia and airway remodeling of asthma (see Remodeling-Associated Cytokines section, below), as insertion of the *GM-CSF* gene in the epithelium of rats caused eosinophil accumulation in their lungs and irreversible fibrosis (50, 51).

## REMODELING-ASSOCIATED CYTOKINES

It has long been known that architectural and structural changes occur in the airways of asthmatic patients. These changes include collagen (type III and IV) and fibronectin deposition, increased thickness of subepithelial basement membrane, goblet cell hyperplasia, increased ASM mass and size, angiogenesis, and fibrosis, all of which collectively contribute to the phenomenon known as airway remodeling. Some of these changes were first described in postmortem airway sections from status asthmaticus victims in the 1960s. More recently, airway remodeling was reported in patients with mild asthma and in children with difficult-to-treat asthma (52). The functional consequences of airway remodeling include persistent AHR and mucous hypersecretion, which contribute to increased susceptibility to asthma exacerbations. The mechanisms involved in airway remodeling are poorly understood, but research in the past three to five years suggests that the balance between matrix metalloproteinases and tissue inhibitors of metalloproteinases may play a role in this process. Moreover, the increase in ASM content, along with a change in the phenotype of fibroblasts to contractile myofibroblasts, may explain the permanent reduction in airway caliber, which is steroid insensitive and typical in patients with severe forms of the disease. The predominant remodeling-associated cytokines include TGF-β, PDGF, IL-6, IL-11, IL-13, IL-17, and IL-25 (**Figure 2**).

TGF-β is a potent profibrotic cytokine. Major sources of TGF-β include fibroblasts, eosinophils, and epithelial cells. However, macrophages, monocytes, neutrophils, ASM cells, and lymphocytes also produce this cytokine. TGF-β is detected in increased concentrations in baseline asthmatic BAL fluid before allergen challenge, and its levels increase even more after allergen challenge. Furthermore, TGF-β exerts an important influence on the turnover of extracellular matrix proteins. In in vitro tissue culture systems, TGF-β exhibits a pleiotropic nature depending on the cell type, culture conditions, and presence of other cytokines. TGF-β induces the proliferation and release of profibrotic and proinflammatory cytokines in fibroblasts and ASM cells, whereas in monocytes, lymphocytes, and epithelial cells, TGF-β inhibits their proliferation and cytokine release (53, 54). TGF-β is also a potent chemoattractant for many cell types, including monocytes, fibroblasts, and mast cells.

Recently, eosinophils were recognized as one of the most abundant sources of TGF-β not only in the asthmatic airways but also in (*a*) the nasal tissues of patients with nasal polyposis and (*b*) hypereosinophilic patients. Using in situ hybridization and immunocytochemistry, our laboratory has demonstrated TGF-β to be significantly elevated in both mild and severe asthmatics, compared with normal subjects, and we have shown that levels of TGF-β expression correlate with basement membrane thickness and disease severity in these patients (55). Approximately 65% of all TGF-β-positive cells are activated eosinophils, which are localized within the reticular lamina. The local

production of TGF-β by eosinophils may be responsible for the subepithelial fibrosis observed in asthmatics. However, TGF-β can also inhibit eosinophil survival and function and may be involved in the repair process of airway epithelial cells. These effects of TGF-β illustrate the complex actions of this cytokine in asthma.

PDGF is not only a major mitogen but also a remodeling-associated cytokine. Its ability to stimulate proliferation of tissue-structural cells, including fibroblasts, epithelial cells, and vascular smooth muscle cells, is well known, and this cytokine has been implicated in alterations of lung function in several chronic lung diseases. Fibroblasts from asthmatic patients show enhanced responsiveness to PDGF, and it is known to activate fibroblasts to proliferate, secrete collagen, and contract collagen lattices (56). Once again, eosinophils are the predominant cellular sources of this cytokine. However, platelets, macrophages, airway epithelial and endothelial cells, vascular smooth muscle cells, and fibroblasts are also known to secrete PDGF. PDGF can be induced by both mechanical and oxidative stress as well as by exposure of cells to various cytokines including IFN-γ, TNF-α, IL-1, and TGF-β. Although PDGF plays an important role in airway remodeling, it is thought that this growth factor is likely to act in concert with other remodeling cytokines, in particular TGF-β, to alter the structural makeup of the airway wall in asthmatic airways.

Another remodeling-associated cytokine is IL-6. IL-6 was first noted for its antiviral activity and for its growth-promoting effects on B cells. IL-6 is produced by macrophages, monocytes, T and B cells, fibroblasts, epithelial cells, and endothelial cells, as well as ASM cells and eosinophils. This cytokine is consistently found in high concentrations in biological fluids and tissues from both animal models of allergic disease and asthmatic patients, but its exact role in asthma remains unclear. IL-6 can stimulate T and B cells' production of Th2 cytokines (57), thereby contributing to the generation and/or perpetuation of Th2-driven inflammation. Also, IL-6 is a potent stimulant of the acute-phase allergic response, and it was recently shown to be a potent smooth muscle mitogen. Mice overexpressing IL-6 in their airways have subepithelial fibrosis, collagen deposition, and increased accumulation of α smooth muscle actin–containing cells, but they do not have eosinophilia, mucous cell metaplasia, or AHR (58).

IL-11 and IL-13 have recently received much attention as key remodeling-associated cytokines because they are thought not only to cause fibrosis and collagen deposition but also to induce myofibroblast hyperplasia, airway obstruction, and AHR. Much of what is known about the role of these cytokines in airway remodeling comes from studies using transgenic mice. Histological analysis of mice in whose lungs IL-11 or IL-13 was constitutively overexpressed resulted in airway wall thickening, enlarged alveoli, subepithelial and adventitial tissue fibrosis, collagen I and III deposition, and increased numbers of contractile and proinflammatory cells when compared with littermate controls (59–61). In addition, IL-11 and IL-13 transgenic mice had baseline airway obstruction and were more responsive to methacholine challenge (62). Sources of IL-11 and IL-13 include epithelial cells, fibroblasts, eosinophils, and smooth muscle cells. Recent evidence suggests that one mechanism by which IL-13 induces tissue fibrosis is the selective stimulation and activation of TGF-β production (59).

We recently confirmed that the results obtained in IL-11-transgenic mice also hold true for human asthma. Using immunocytochemistry and in situ hybridization, we have demonstrated increased expression of IL-11 mRNA and protein in the epithelial and subepithelial layers of the airway walls in patients with severe asthma, but not in mild asthmatics or healthy controls (63). Furthermore, IL-11 expression was inversely correlated with the forced expiratory volume in the first second ($FEV_1$) in severe asthmatics, and the IL-11 mRNA–positive cells were localized to epithelial cells and major basic protein–positive eosinophils (64). A proposed mechanism by which IL-11 can induce

these structural changes in the airways may be promotion of the synthesis of TIMP-1 (tissue inhibitor of metalloproteinases-1), which is elevated in sputum and biopsy samples from asthmatic patients and correlates with asthmatic airway obstruction (65). Although these studies clearly support a role for IL-11 in airway remodeling, other studies (61) suggest that levels of IL-11 may in fact increase as a result of normal airway repair. IL-11-transgenic mice exhibited selective inhibition of antigen-induced airway and parenchymal eosinophilia, Th2 inflammation, Th2-cytokine production, and VCAM-1 gene expression (61). These conflicting data point to the dual nature of IL-11, which acts both as a cytokine that promotes healing and as a cytokine that is capable of inducing local tissue fibrosis.

Other remodeling-associated cytokines recently described in the literature include IL-17 and IL-25, which are potent proinflammatory cytokines. IL-17 and IL-17A are produced exclusively by activated Th lymphocytes, whereas Th2 cells and mast cells secrete IL-25. Expression of IL-17 is markedly increased in asthmatic subjects (66). In mice, systemic overexpression of IL-17 induces neutrophilia via direct in vivo stimulation of IL-6 and IL-8, whereas overexpression of IL-25 results in increased Th2-cytokine gene expression (particularly IL-4, IL-5, IL-10, and IL-13), increased mucous production, elevated serum IgE and IgG1, and tissue eosinophilia (24). These pathological changes are not restricted to the lungs.

## IMMUNOMODULATORY CYTOKINES

It is now generally accepted that adult atopic disease is characterized by the expression of T cell immunity to common airborne environmental allergens, which is polarized toward the Th2-cytokine profile; in nonatopics, Th1-skewed immunity is observed. As a result, shifting the balance from Th2 to Th1 immunomodulatory cytokines (**Figure 3**) such as IL-10, IL-12, and IFN-$\gamma$ may be important for the treatment of allergic inflammation.

IL-10 is primarily known as an inhibitory cytokine; however, it can exert both immunosuppressive and immunostimulatory effects. IL-10 was originally identified as a product of murine Th2 cells, but in humans IL-10 is produced by Th0, Th1, and Th2 cells and also by activated monocytes, mast cells, and macrophages (43). In normal lungs, alveolar macrophages are the major source of IL-10, but IL-10's expression is significantly reduced in asthmatic individuals (67, 68). IL-10 curtails the effects of proinflammatory cytokines (e.g., TNF-$\alpha$, IL-1$\beta$, IL-6, IL-8, and MIP-1$\alpha$) released during an allergic reaction. In addition, IL-10 can inhibit eosinophil survival and migration by preventing the release of chemoattractants such as RANTES and IL-8 from human ASM cells (68). Moreover, IL-10 inhibits allergen-induced eosinophilia in sensitized mice and dampens their late-phase response to allergen challenge (47, 69). Its other actions include downregulation of the IL-4-induced isotype switching of activated B cells (25), which prevents IgE synthesis. IL-10 may inhibit Th2-driven inflammation, and it is also known to inhibit the differentiation of Th1 cells, thereby preventing the release of IFN-$\gamma$ and IL-2. Moreover, IL-10 can interfere with the functions of monocytes and macrophages. IL-10 can inhibit MHC class II expression on the surface of antigen-presenting cells and can prevent superoxide and nitric oxide (NO) release from inflammatory cells (70).

Other members of the IL-10 family of cytokines are IL-19, IL-20, IL-22, and IL-24. Like IL-10, they are considered to be anti-inflammatory cytokines and are produced by a variety of cell types, including monocytes, keratinocytes, mast cells, and lymphocytes. However, unlike IL-10, these cytokines cannot inhibit the effects of proinflammatory mediators involved in allergic response. IL-19, IL-20, and IL-24 have not been extensively studied; however, studies of IL-22 have shown that this cytokine is involved in the induction of IgE-independent acute-phase response signals (71).

IFN-$\gamma$ is the most important cytokine in cell-mediated immunity; it controls the balance

of Th1/Th2 development (**Figure 1**). IFN-γ is produced by Th1 cells and has an inhibitory effect on Th2 cells. IFN-γ inhibits allergic responses by preventing isotype switching of IgE and IgE production in B cells (72). The main sources of IFN-γ are Th cells. However, IFN-γ can also be produced by cytotoxic T cells and natural killer (NK) cells. In addition to its potent inhibitory effect on Th2 cells, IFN-γ stimulates de novo expression of MHC class II molecules on epithelial and endothelial cells and upregulates their expression on macrophages/monocytes and on dendritic cells. Importantly, IFN-γ stimulates monocytes, NK cells, and neutrophils to increase their cytokine production, phagocytosis, adherence, respiratory burst, and NO production, thereby promoting cell-mediated cytotoxic responses at the site of inflammation.

In sensitized and allergen-challenged mice, nebulized IFN-γ prevents allergen-induced increase in Th2 cytokine production, AHR, and lung eosinophilia (73). This has been proposed to occur via upregulation of IL-10. T cell production of IFN-γ is reduced in the BAL of asthmatic patients, and the levels of IFN-γ correlate closely with disease severity (74). Clinical trials with IFN-γ in humans have proved disappointing, as no significant improvement in lung function was observed in steroid-dependent asthmatics despite reduced numbers of eosinophils in the blood (75).

IL-12 is produced by antigen-presenting cells including B cells, monocytes, macrophages, Langerhans cells, and dendritic cells, as well as neutrophils and mast cells. IL-12 promotes T cell differentiation toward a Th1-mediated response by stimulating NK and T cells to produce IFN-γ while suppressing the expansion and differentiation of IL-4-secreting Th2 cells (76). The biologically active form of IL-12 is a heterodimer consisting of the p40 subunit and the p35 subunit, which are expressed by different genes. The effects of IL-12 have been extensively studied in small animal models of allergic inflammation and consistently demonstrate that this cytokine is involved in reduction of allergen-specific IgE, abolition of AHR, and airway eosinophilia (77, 78). However, this effect of IL-12 is critically dependent on the timing of its administration. The most effective protection against allergen-induced inflammation is observed when IL-12 is administered early in the active sensitization process and thus when it can act in synergy with IL-18 (79). IL-18, also known as IFN-γ-inducing factor, is a potent inducer of IFN-γ production by T cells, NK cells, and B cells (80). In asthmatic patients, IL-12 is significantly reduced in peripheral blood and in airway biopsy specimens, compared with healthy controls. IL-12 mRNA levels increase in biopsies of asthmatic patients following treatment with corticosteroids (31), and although the administration of IL-12 has failed to show any effects on AHR or the late-phase asthmatic responses in mild asthmatics, IL-12 is effective in suppressing blood and sputum eosinophilia in these patients (81).

## CHEMOKINES

Chemokines are small cytokines (8–10 kDa) involved primarily in a process called chemotaxis, whereby they attract and regulate leukocyte trafficking into the tissues by binding specific seven-transmembrane-spanning G protein–coupled receptors (**Figure 4**). To date, more than 40 chemokines have been described and have been classified into four subclasses according to their structure: CXC, CC, C, and CX3C. The two main groups are CXC (α chemokines) and CC (β chemokines). CXC chemokines include IL-8 and IP-10, which primarily target neutrophils. Eotaxin, RANTES, MCP-1–MCP-4, macrophage inhibitory protein (MIP)-1α, and MIP-1β are typical CC chemokines, which target monocytes, T cells, and eosinophils. For this reason, CC chemokines are thought to have the greatest relevance in the pathogenesis of asthma. Levels of chemokines in both BAL and biopsy samples of asthmatics are higher than in control patients (43).

Eotaxin and RANTES, acting in synergy with IL-5, are the most important

eosinophil chemoattractants in allergic inflammation. These chemokines are produced by the majority of inflammatory cells, and recently their expression was described in ASM cells and fibroblasts. Unlike RANTES, which binds many chemokine receptors (CCRs) including CCR1, CCR3, and CCR5, eotaxin binds specifically to CCR3, which is highly expressed on and has selective chemoattractant activity for eosinophils (82). In addition, eotaxin induces α4- and β1-integrin expression on eosinophils, allowing for firm adhesion of eosinophils to endothelium and transmigration into the site of inflammation (**Figure 4**). More importantly, eotaxin and RANTES are produced in high concentrations in the lungs of asthmatic patients.

MCPs and MIPs are monocyte/macrophage chemoattractants and activating factors. To date, four MCPs (MCP-1–MCP–4) and two MIPs (MIP-1α and -1β) have been described. Increased levels of MCP-1 and MCP-3 have been detected in BAL of asthmatic patients (83), and increased expression of MCP-4 has been reported in the sputum (84), BAL (85), bronchial mucosa (61), and small airways (64) of asthmatics as well as in the noses of patients with allergic rhinitis (65). MCP-1 binds CCR2, MCP-2 binds CCR3, MCP-3 binds CCR1 and CCR3, and MCP-4 binds CCR2, CCR3, and CCR5. MCP-1 immunoreactivity has been demonstrated in human eosinophils; furthermore, MCP-2, MCP-3, and, in particular, MCP-4 are also thought to be potent eosinophil chemoattractants (85). Moreover, MCP-4 attracts not only eosinophils and monocytes but also lymphocytes and basophils. MIP-1α binds CCR1 and CCR5, and MIP-1β binds CCR5 exclusively.

Although the primary role of chemokines is chemotaxis, chemokines have a variety of other functions, including direct effects on T cell differentiation. MIP-1α, MIP-1β, and RANTES can promote the development of IFN-γ-producing Th1 cells by stimulating IL-12 production from antigen-producing cells. However, MCP-1, MCP-2, MCP-3, and MCP-4 can increase T cell production of IL-4 and can decrease antigen-producing cells' production of IL-12, resulting in a Th2 phenotype.

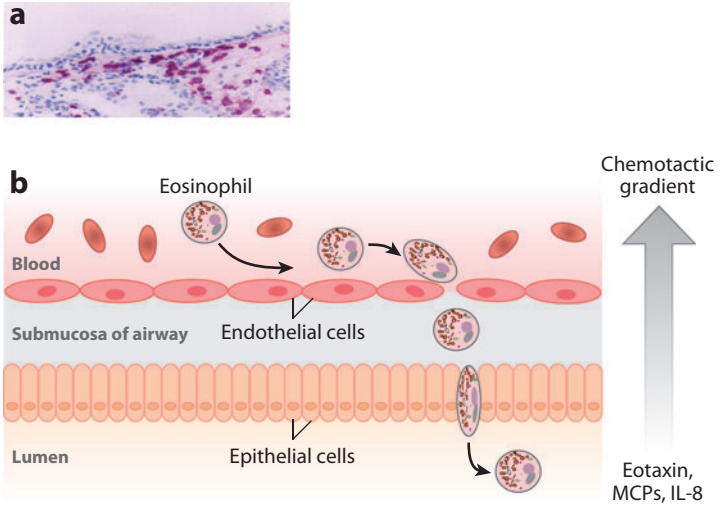


**Figure 4**

(*a*) Histology showing real eosinophils accumulating in the lung. (*b*) Illustration of the role of chemokines in the pathogenesis of asthma. MCP, monocyte chemoattractant protein.

## CYTOKINES, ASTHMA, AND INFECTION

The reasons for the increasing prevalence of allergic respiratory diseases in developed countries and in undeveloped countries that develop a Western lifestyle remain unclear. For many years, lower respiratory tract infections in early life have been recognized as primary triggers of asthma exacerbations in young children. Using both epidemiological and virology data, prospective studies have convincingly shown that viral and not bacterial respiratory infections precipitate reactive airway symptoms (86). It is now believed that the development of bacteria-induced, nonwheezing lower respiratory tract infection in childhood may protect against the development of atopy and asthma in later life. This line of thought comes from experimental evidence that suggests that the principal trigger for normal postnatal maturation of the immune system is the commensal microbial flora, particularly those of the gastrointestinal tract. Microbial exposure helps to skew the

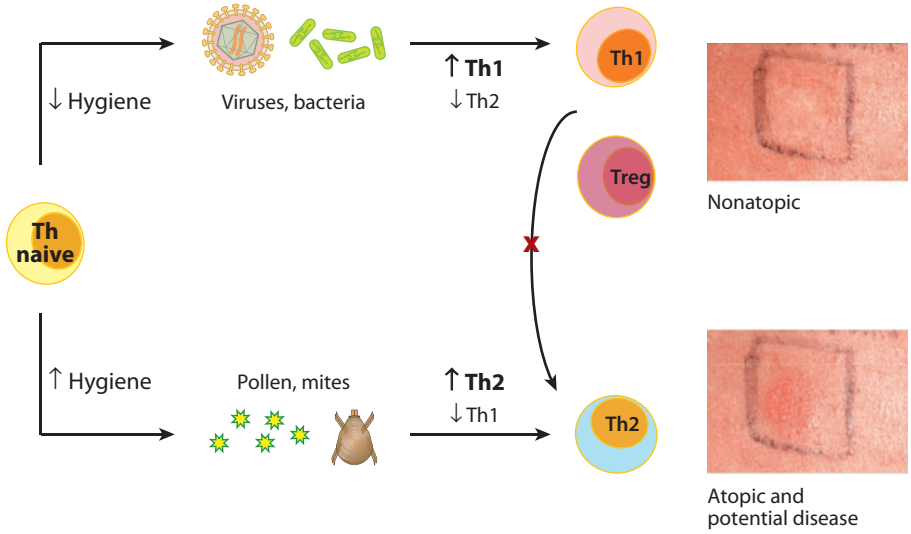


**Figure 5**

The possible mechanism of the hygiene hypothesis and the effect of early infections on cytokine gene expression. Abbreviations: Th, T helper cell; Treg, T regulatory cell.

immune response away from allergic phenotype and toward the normal adult nonatopic immune response (87). The longer the immune system takes to adapt postnatally to its functionally mature state, the greater is the risk for allergic sensitization (88).

The hygiene hypothesis suggests that decreasing levels of exposure to infections and/or commensal microbial stimuli in developed countries, particularly during the induction of primary Th1/Th2 responses to allergens in early life, may be responsible for the increased prevalence of asthma (**Figure 5**). There is ample epidemiological evidence to support this hypothesis (89). The reported increase in atopy inversely correlates with a steady decline in the extent to which people in Western societies are exposed to infectious diseases such as whooping cough, measles, tuberculosis, and influenza (90). Allergic diseases appear to increase with advancing socioeconomic development and occur more frequently in industrialized countries than in developing areas (91), and spending one's early years resident on a farm protects against the development of allergies (92, 93).

Bacterial lipopolysaccharide (LPS) or endotoxin has been suggested as a potential mediator of these effects. LPS is a major component of the outer membrane of ubiquitous gram-negative bacteria. Gram-negative infections make up a significant proportion of clinical respiratory tract infections among children in early life; thus, there is ongoing and chronic environmental exposure to gram-negative organisms and their components/products. In common house dust, LPS makes up a significant proportion of dust weight, and a significant correlation has been reported between domestic LPS exposure and clinical severity of asthma in adults (94). The first direct in vivo evidence that environmental exposure to LPS early in life (before polarized Th cell responses are established) protects against allergen sensitization was reported by Gereda and colleagues (95), who have demonstrated that (*a*) the homes of allergen-sensitive infants (9–24 months of age) contain lower concentrations of LPS in house dust than do the homes of nonsensitive infants and (*b*) the lower concentrations are associated with reduced proportions of IFN-γ-producing Th cells. Consistent with this

hypothesis, three distinct LPS phenotypes in humans have been described—sensitive, intermediate, and hyporesponsive—on the basis of reduction in $FEV_1$ following inhalation of increasing doses of LPS and in vitro production of IL-6 and IL-8 from peripheral blood monocytes and alveolar macrophages (95).

Experimental results in animal models of asthma have supported the hygiene hypothesis. They have shown that treatment with microbes [e.g., BCG (96) and *Lactobacillus* (97)] or microbial products [LPS (98) and CpG DNA (99, 100)] inhibits allergic sensitization, eosinophilic inflammation, and AHR in these animals. In a similar animal model of allergic disease, we have shown that both the timing of exposure and the dose are critical to the in vivo effect of LPS (98). That study demonstrated that, although LPS exposure during early sensitization protects against the development of IgE and consequent allergic inflammation, in marked contrast, exposure after allergen challenge further exacerbates the allergic response.

Toll is a *Drosophila* receptor that is involved in antifungal immune responses. Toll-like receptors (TLRs) are a large family of evolutionarily conserved receptors from Toll that sense invasion by microorganisms through the recognition of specific pathogen-associated molecule patterns and that produce immediate innate responses. To date, 10 TLRs (TLR1–10) have been identified in humans and in mice (88) TLRs are single-transmembrane-domain receptors that have a cytoplasmic signaling portion homologous to the IL-1 receptor. Although the TLRs differ in their extracellular domain structure, similar cytoplasmic domains allow TLRs to use the same signaling molecules. All TLRs signal through an adaptor protein known as myeloid differentiation factor 88 (MyD88). Following activation, MyD88 recruits the IL-1R/IL-1R-associated protein kinase (IRAK) complex to the TLR; IRAK becomes phosphorylated and then activates the TNF receptor–associated factor 6. This process leads to activation of JNK (c-Jun N-terminal kinase), MAPK (mitogen-activated protein kinase), and NF-κB (nuclear factor–kappa B) pathways, leading to a cascade of events including the release of cytokines and the activation of antigen-presenting cells.

Different TLRs recognize different ligands. TLR3 is a cell-surface receptor for double-stranded RNA; hence, it may be implicated in viral recognition. TLR5 is specific for bacterial flagellin, whereas TLR9 is a receptor for unmethylated CpG motifs, which are abundant in bacterial DNA. In mammals, TLR4 is the principal receptor responsible for LPS-induced signal transduction (101). Recognition of LPS by TLR4 is aided by two accessory proteins: CD14 and MD-2. TLR4 is expressed at particularly high levels by cells of the innate immune system, such as monocytes, dendritic cells, macrophages, and endothelial cells (102–105). TLR4 expression is thought to be related to LPS sensitivity (106), and it was recently demonstrated in murine macrophages that TLR expression and function decline with age (107, 108).

We have shown that bacterial LPS can prevent local allergen-induced inflammation in the nasal mucosa of atopic children. This occurs by downregulation of local Th2 and by upregulation of Th1 cytokines in the tissue, proliferation, and activation of $TLR4^+IL10^+$ and $CD25^+$ Th cells, as well as by increased expression of anti-inflammatory cytokine IL-10 (109). These events occur locally without systemic recruitment of inflammatory cells and are orchestrated through the TLR4-dependent pathway. TLR4 is an important bridge between innate and adaptive immunity that potentially drives the molecular mechanisms governing the hygiene hypothesis and that may help explain why reduced exposure to bacterial products may lead to delayed or skewed development of the immune system and more atopic disease.

## CONCLUSIONS

Bronchial asthma is a complex, chronic disease of the airways that is characterized by reversible AHR, airway remodeling, and inflammation. These pathological and physiological changes

occur even in mild asthmatics and can be detected in asthmatic children. Within the past decade, one of the most striking advances in study of asthma has been the recognition that cytokines and chemokines play an integral role in orchestrating, perpetuating, and amplifying the underlying processes of this disease. Therapy for asthma may lie in specific targeting of cytokine and chemokine receptors rather than in global immunosuppression. Additionally, it has become clear that bacterial products play a role in the maturation of early immune responses and that they can modulate allergic inflammation in young children. Only by understanding the immunobiology of asthma can we begin to provide a rational basis of novel drug design and make progress in identifying those individuals at risk for this disease.

## DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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