Asthma is a highly prevalent disease that involves a complex interplay of environmental factors, airflow obstruction, bronchial hyperresponsiveness, and inflammation. The dominant feature that leads to clinical symptoms is smooth muscle contraction and inflammation, which results in narrowing of the airway and obstruction.\textsuperscript{1,2} Numerous triggers can induce bronchoconstriction, including allergic responses, respiratory infections, exercise, irritants, and nonsteroidal anti-inflammatory drugs in select patients\textsuperscript{1,2}. Persistent inflammation in the airway may lead to structural changes, such as mucus hypersecretion, smooth muscle hyperplasia, subepithelial fibrosis, blood vessel proliferation, and infiltration of inflammatory cells.\textsuperscript{1,2}

The concepts underlying asthma pathogenesis have dramatically evolved over the past 25 years, and understanding of this complex disease continues to increase. It is now clear that asthma is not a single disease, but rather a syndrome that can be caused by multiple biologic mechanisms. Thus, asthma encompasses many disease variants with different etiologic and pathophysiologic factors.

Several approaches have been used to classify variants of asthma with the goal of maximizing the efficacy of treatment. Clinically, asthma can be described based on symptoms that are either intermittent or persistent, and these symptoms are further classified in terms of severity (ie, mild, moderate, or severe).\textsuperscript{1} However, this classification system does not address the underlying biologic processes that drive the disease.

Recent efforts have attempted to classify asthma according to objective phenotypes.\textsuperscript{4} Analysis of these phenotypes is based on observable characteristics, such as symptoms, biochemical properties, immunologic features, histologic and morphologic characteristics of tissue, and response to treatment. Lotvall et al\textsuperscript{5} described a classification scheme of asthma endotypes, summarized in Figure 1, that is based on the use of these criteria.

There are likely to be molecular differences even within endotypes, as well as overlap in inflammatory features between endotypes—highlighting the complexity of this disease and the need for continued research. Nevertheless, a common thread underlying all endotypes is the presence of airway inflammation, though each endotype has distinct immunologic features. The present review focuses on the inflammatory response in patients with allergic asthma. The mechanisms described in this review also apply to other endotypes.

Orchestrated Interplay
The inflammatory response in the airways of patients with asthma involves an orchestrated interplay of the respiratory epithelium, innate immune system, and adaptive immunity that initiates and drives a chronic inflammatory response (Figure 2).\textsuperscript{1,2,6,7} Central to this process is an interaction between genes and environment, resulting in an abnormal immune response to allergens and other environmental triggers in genetically susceptible individuals.\textsuperscript{8,9}

The immunohistopathologic features of asthma include epithelial injury and infiltration of inflammatory cells, consisting of eosinophils, lymphocytes, mast cells, and phagocytes.\textsuperscript{1,2,6,7} Inflammatory mediators released by these cells are the effectors of chronic inflammation. These mediators include cytokines and other products that are classified into the following groups (summarized in Figure 4): lymphokines (immunomodulatory cytokines released by T cells), proinflammatory cytokines (cytokines that promote and amplify the inflammatory response), chemokines (cytokines that are chemoattractants for leukocytes), growth factors (factors that promote cell survival), and eicosanoids (lipid mediators that have multiple effects in the airway).\textsuperscript{10} The products released from leukocytes and epithelial cells induce bronchospasm, damage the epithelium, stimulate airway cells, and recruit additional leukocytes—creating a cycle of inflammation that becomes chronic.\textsuperscript{10}

Over time, persistent changes in the structure of the airway can occur, such as subepithelial fibrosis, mucus hypersecretion and goblet cell hyperplasia,
The respiratory epithelium, formerly thought to serve only as a barrier and medium for gas transfer, is now known to play a central role in the inflammatory response. It serves as a primary interface between the external environment and the host, and it is exposed to numerous stimuli, such as allergens, infectious agents, pollutants, and oxidants. As such, the respiratory epithelium is an integral part of innate immunity and the inflammatory response, and it is capable of producing numerous mediators that can prime and activate many arms of the immune system.\(^{11,12}\) Numerous stimuli are capable of eliciting an inflammatory response from epithelial cells. Components of microbes, including nucleic acids and glycoproteins, bind to such pattern recognition receptors as toll-like receptors to stimulate production of cytokines and chemokines.\(^{11-13}\) Pollutants and oxidants can alter the structure and activity of proteins, lipids, and nucleic acids to affect signaling pathways or to injure cells.\(^{14}\) Proteases, including those found in many allergens, can activate immune signal transduction pathways by modulating the activity of protease activated receptors.\(^{14}\) These stimuli modulate the functions of the airway epithelium and induce the production of mediators that attract and activate leukocytes and augment the development of an allergic response (Figure 3).

One of the central cytokines whose production is stimulated by the epithelium is thymic stromal lymphopoietin (TSLP), which induces key changes in dendritic cells, the antigen-presenting cells that deliver allergens to T cells in the first phase of an allergic response. TSLP induces the release of chemokine ligand 17 (CCL17) and CCL22 from dendritic cells, an important process in recruiting T cells to the airways. In addition, TSLP increases the expression of CXCR4 ligand (CXCR4L), a receptor that is important in skewing the dendritic cell-mediated activation of T cells toward an allergic response. Thymic...
stromal lymphopoietin—
in concert with other epithelial-derived inflammatory cytokines, such as tumor necrosis factor...
[TNF-α] and interleukin [IL-1β]—can also activate mast cells. Mast cells are one of the principal leukocytes that participate in the allergic response. 10

The airway epithelium produces large amounts of inflammatory cytokines, including TNF-α, IL-1β, and IL-6. 10 These proteins have widespread effects on a wide variety of cells, including leukocytes, in the immune system. The effects serve to upregulate inflammatory genes, increase the release of cytokines and chemokines, and expand inflammatory cell numbers. 10 In addition, airway cells are a prime source of chemokines, potent chemoattractants for various leukocytes.

Chemokines play an important role in the recruitment of inflammatory cells from circulation to the airways. The cell types recruited depend on the specific chemokine receptor expressed on inflammatory cells. For example, CCL2 (also known as monocyte chemotactic protein 1 [MCP-1]) activates chemokine receptor 2 (CCR2) molecules on monocytes and T cells. 10 Chemokine ligand 11 (ie, eotaxin) acts as a potent chemoattractant for eosinophils by binding to CCR3. 10 Chemokine ligand 5 (ie, RANTES) can bind to CCR3 and CCR5 (which are expressed on T cells, eosinophils, and macrophages) and, thus, attracts a large number of inflammatory cells. 10

The chemokine ligand CXCL8 (ie, IL-8) activates the receptor CXCR1 on neutrophils. 10 After leukocytes travel to the airway, they produce inflammatory...

**Figure 2.** Cycle of chronic inflammation in patients with asthma. Allergic inflammation develops from an interplay between the respiratory epithelium and leukocytes. Environmental and inflammatory stimuli induce the production of mediators from the airway epithelium, which activates and recruits inflammatory cells. Inflammatory cells infiltrate the lungs and release mediators that augment the inflammatory response in the epithelium, creating a cycle of chronic inflammation. This process causes bronchoconstriction and epithelial damage, and it can result in remodeling of the airway. Abbreviation: IgE, immunoglobulin E.

References 1, 2, 6, and 7.

**Figure 3.** Pathogenesis of allergic asthmatic inflammation. Allergens are endocytosed by antigen presenting cells (APCs) and presented to naive T cells. Environmental and inflammatory factors activate the respiratory epithelium to release thymic stromal lymphopoietin (TSLP) and other inflammatory mediators that recruit leukocytes to the lung and skew the function of dendritic cells toward an allergic response. Dendritic cells induce the differentiation of T cells into Th2 helper 2 (Th2)-specific helper cells, as well as Th17 cells. The Th2 cells induce immunoglobulin E (IgE) antibody production from B cells via interleukin 4 (IL-4) and IL-13 stimulation. Immunoglobulin E binds to receptors on the surfaces of mast cells and basophils and, in the presence of allergen, release mediators that induce bronchoconstriction and enhance the inflammatory response. Production of IL-5 from Th2 cells increases eosinophil levels. Inflammatory mediators released from eosinophils, T cells, macrophages, and neutrophils result in damage to the airway, bronchoconstriction, stimulation of epithelial cell inflammatory pathways, and remodeling of the lung. Abbreviations: CCL, chemokine ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; PGD2, prostaglandin D2; SCF, stem cell factor; TNF-α, tumor necrosis factor-alpha.

References 8, 10, 11, and 14.
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<td></td>
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<tr>
<td>IL-4</td>
<td>T cells</td>
<td>Increases production of IgE, increases number of Th2 cells</td>
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<tr>
<td>IL-17</td>
<td>T cells</td>
<td>Increases neutrophil number, induces production of cytokines by airway epithelium</td>
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<td>TSLP</td>
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<tr>
<td>PGD₂</td>
<td>Mast cells</td>
<td>Airway hyperreactivity</td>
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Figure 4. Key inflammatory mediators in the pathogenesis of asthmatic inflammation. Abbreviations: CCL, chemokine ligand; CXCL, chemokine CXC ligand; EGF, epithelial cell growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IgE, immunoglobulin E; IL, interleukin; PGD₂, prostaglandin D₂; SCF, stem cell factor; TGF-b, transforming growth factor b; Th2, T-helper 2 lymphocyte; TNF-a, tumor necrosis factor-alpha; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor. References 7, 8, 10, 11-13, 16.
cytokines, which, in turn, act as potent activators of the inflammatory response in epithelial cells. This activation results in a perpetual cycle of chronic inflammation in which the epithelium and leukocytes activate each other.

The epithelium also releases growth factors that augment the inflammatory response and induce structural changes and remodeling of the airways. Granulocyte-macrophage colony-stimulating factor (GM-CSF) prolongs eosinophil and neutrophil survival, while stem cell factor (SCF) increases the survival and activation of mast cells. Vascular endothelial growth factor (VEGF) stimulates angiogenesis and may contribute to vascular leak and airway edema. Transforming growth factor β (TGF-β) is a multifunctional growth factor that induces proliferation of fibroblasts and airway smooth muscle cells, as well as the deposition of extracellular matrix components. In conjunction with cytokines, these factors play a crucial role in initiating and propagating the chronic inflammatory response and in the remodeling of the airway that occurs over time in patients with asthma.

**Allergic Response and T-Helper 2 Lymphocytes**

The central component of allergic asthma is the development of an immunoglobulin E (IgE) antibody-mediated response to allergens that requires the interaction of a number of leukocytes. Inhaled allergens are endocytosed by antigen presenting cells (APCs), which are usually dendritic cells in the airways that function in surveilling the environment for pathogens. Dendritic cells travel to lymph nodes and present antigens on the cell surface via major histocompatibility complex proteins; they also interact with CD4+ naive T cells that contain receptors specific to the antigen.

Dendritic cells are crucial to the development of an immune response and serve as gatekeepers of the immune system. Through the production of an assortment of mediators and cell surface molecules, dendritic cells have the capability of inducing tolerance or eliciting an immune response. Dendritic cells can further control the nature of the immune response by promoting differentiation of CD4+ T cells into various types of T-helper (Th) cells with specific functions. The stimulation of 1 type of response vs another type of response is based on the nature of the mediators produced by dendritic cells, which, in turn, is influenced by products of the epithelium (ie, TSLP and other cytokines) and other signals from the environment. Expression of IL-4, OX40L, and the cluster of differentiation (CD) marker CD86 promote differentiation of T cells into T-helper 2 (Th2)-specific helper cells, which are central to allergic diathesis.

T-helper 2 lymphocytes drive the formation of allergic reaction and activation of inflammatory cells via the production of cytokines crucial to allergic disease. The T-cell receptors and co-stimulatory molecules on the surfaces of Th2 cells engage allergen-specific B cells. Production of IL-4 and IL-13 promote antibody class switching in B cells to synthesize IgE antibodies. The Th2 cells and allergen-specific B cells can differentiate into memory cells, facilitating and quickening future allergic responses.

Immunoglobulin E is secreted from B cells into circulation, where it binds to high-affinity FceRI receptors on the surfaces of mast cells (in interstitial tissue) and basophils. Immunoglobulin E continues to be synthesized even in the absence of allergen, and IgE is maintained on the surfaces of mast cells and basophils. Upon the next encounter with allergen, the antigen binds to membrane-bound IgE, stimulating release of such mediators as histamine, leukotrienes, and cytokines. Because this process results from the binding of antigen to existing antibody-receptor complexes, an immediate response occurs (ie, within minutes), forming the basis for immediate hypersensitivity reactions.

Other cytokines produced by Th2 cells are capable of activating other leukocytes and playing key roles in allergic inflammation. Interleukin 5 is a potent survival factor for eosinophils, which are central effector cells in patients with asthma. Systemic administration of IL-5 to patients with asthma increases circulating eosinophils and their precursors from the bone marrow. Blockade of IL-5 with monoclonal antibodies in animal studies has reduced eosinophil numbers in the blood and lungs and inhibited allergen-induced asthma. The role of IL-5 in disease in humans is complex and may be more important in patients with certain asthma phenotypes (eg, the severe late-onset hypereosinophilic endotype). T helper cells also release IL-9, which occurs in elevated concentrations in the airways of patients with asthma and in mice with experimentally induced asthma. Interleukin 9 promotes mast cell growth, tissue eosinophilia, and production of other Th2 cytokines.

A class of Th cells known as Th17 cells has recently been identified as a component in asthmatic inflammation. In mouse models, allergen sensitization causes Th17 cells to home to the lungs, where they enhance neutrophilic infiltration and augment Th2-mediated eosinophilic inflammation. T-helper 17 cells secrete IL-17, which has been shown to occur in elevated levels in the airway and blood of patients with asthma. The IL-17 family consists of 6 members (A-F), which emerging evidence suggests are involved in numerous other inflammatory diseases, including rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and psoriasis. Interleukin 17...
upregulates a diverse set of cytokines, chemokines, adhesion molecules, and growth factors. Its exact role in asthma and allergic disease and its interplay with Th2 pathways and other leukocyte pathways are areas of active research with implications for the understanding of disease pathogenesis and treatment.

**Effector Cells in the Inflammatory Response**

Stimulation of T cells and epithelial cells causes the activation and recruitment of other effector leukocytes to the airway, and mediators produced by these cells result in chronic inflammation, tissue damage, and remodeling. Mast cells are the central effector cell in allergic disease and are present in increased numbers in the airways of patients with asthma. Binding of allergen to IgE on the cell surface induces a signal transduction cascade that results in the release of mediators. The release of histamine and prostaglandin D2 (PGD2) results in bronchoconstriction.

Mast cells are also the primary producers of cysteinyl leukotrienes, lipid mediators derived from arachidonic acid. Leukotrienes bind to their G protein-coupled receptors on the cell surfaces of structural airway cells. There they produce smooth muscle contraction, increase vascular permeability of small blood vessels, enhance secretion of mucus, and recruit leukocytes to the airway. Cysteinyl leukotrienes play an important role in asthma, and their inhibition with leukotriene antagonists is effective in the treatment of patients with asthma.

Mast cells also release inflammatory cytokines, chemokines, and proteases that contribute to airway inflammation. These mediators stimulate an inflammatory response in the epithelium, directly damage the airway, and recruit more leukocytes to the airway.

Increased numbers of eosinophils are present in the airways of most patients with asthma. The recruitment, growth, and survival of eosinophils are promoted by factors released from airway epithelial cells, Th2 cells, and mast cells. The Th2 cytokine IL-5 is central to eosinophil survival, as is GM-CSF, which is derived from the epithelium and mast cells. Chemokines, particularly CCL5 and CCL11, recruit eosinophils to the airway. Eosinophils express a variety of proinflammatory cytokines, Th2 cytokines, and chemokines that can activate mast cells and stimulate the epithelium. In addition, eosinophils can present antigen to T cells and release growth factors such as TGF-β—highlighting the importance of eosinophils in multiple facets of asthmatic inflammation. The role of eosinophils in asthma may vary with different phenotypes, and patients with severe asthma are noted to have elevated numbers of eosinophils.

Phagocytes are also present in asthmatic airways, though their role is not well-defined. They may be more prevalent in certain phenotypes than in others. Macrophages are present in high numbers in the airways and synthesize many inflammatory cytokines and chemokines. Neutrophils may occur in increased numbers in the airways of patients with severe asthma, particularly in smokers. Their pathogenic role remains to be determined, but it may account for a lack of glucocorticoid effects in some patients.

T cells are now recognized to play important effector roles in patients with asthma. Interleukin 13 produced from Th2 cells has been the focus of much research as a therapeutic target. It induces airway hyperresponsiveness and has numerous effects on structure, such as subepithelial fibrosis, airway smooth muscle proliferation, and goblet cell hyperplasia. Interleukin 13 induces inflammation by acting primarily on the airway epithelium, and it increases eosinophil numbers by up-regulating multiple chemokines, including CCL11. Induction of chemokines may also be important in lung fibrosis, as suggested by mouse studies demonstrating that the blockade of CCL2, CCL3, and CCL6 abrogates lung remodeling.

Furthermore, IL-13 has been proposed to be associated with glucocorticoid resistance, with the level of IL-13 being elevated in patients with glucocorticoid-insensitive asthma. Glucocorticoids regulate the level of many cytokines and chemokines at transcriptional and posttranscriptional levels, and research has shown that IL-13 can directly affect the phosphorylation of the glucocorticoid receptor to alter its function. Thus, IL-13 provides an attractive therapeutic target that might be beneficial to consider in many asthma phenotypes, including steroid-insensitive asthma.
Asthma is a chronic inflammatory disease that comprises multiple phenotypes and inflammatory triggers. These phenotypes share common inflammatory features, though their specific immunologic pathways may differ mechanistically. As we dissect these mechanisms at the molecular level, the treatment of patients with asthma can be tailored to specific phenotypes. Targeting the mediators and cells described in the present review represent the basis of current asthma treatment and highlight the potential for development of novel therapeutic agents in the future.

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