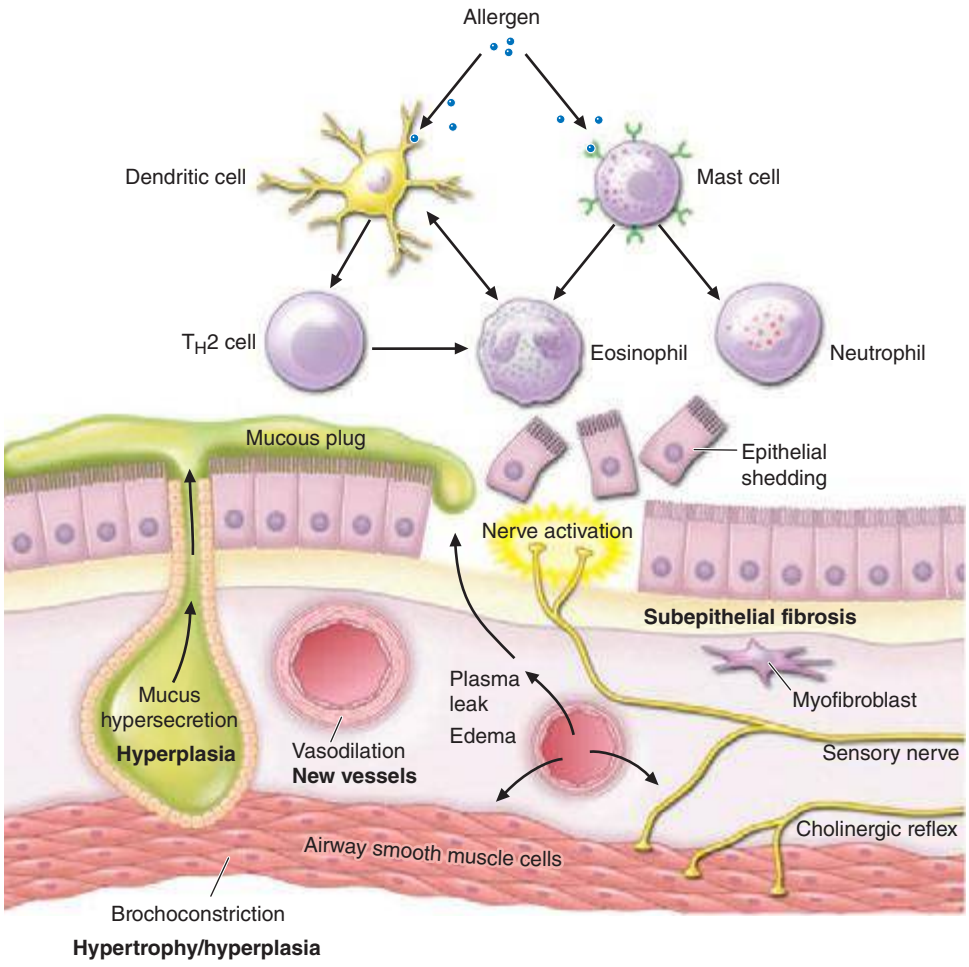

FIGURE 309-3 **The pathophysiology of asthma is complex** with participation of several interacting inflammatory cells, which result in acute and chronic inflammatory effects on the airway.

EOSINOPHILS Eosinophil infiltration is a characteristic feature of asthmatic airways. Allergen inhalation results in a marked increase in activated eosinophils in the airways at the time of the late reaction. Eosinophils are linked to the development of AHR through the release of basic proteins and oxygen-derived free radicals. Eosinophil recruitment involves adhesion of eosinophils to vascular endothelial cells in the airway circulation due to interaction between adhesion molecules, migration into the submucosa under the direction of chemokines, and their subsequent activation and prolonged survival. Blocking antibodies to IL-5 causes a profound and prolonged reduction in circulating and sputum eosinophils, but is not associated with reduced AHR or asthma symptoms, although in selected patients with steroid-resistant airway eosinophils, there is a reduction in exacerbations. Eosinophils may be important in release of growth factors involved in airway remodeling and in exacerbations but probably not in AHR.

NEUTROPHILS Increased numbers of activated neutrophils are found in sputum and airways of some patients with severe asthma and during exacerbations, although there is a proportion of patients even with mild or moderate asthma who have a predominance of neutrophils. The roles of neutrophils in asthma that are resistant to the anti-inflammatory effects of corticosteroids are currently unknown.

T LYMPHOCYTES 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 a mast cell population in the airways. The naïve immune system and the immune system of asthmatics are skewed to express the T_H2 phenotype, whereas in normal airways, T_H1 cells predominate. T_H2 cells, through the release of IL-5, are associated with eosinophilic inflammation and, through the release of IL-4 and IL-13, are associated with increased IgE formation. Recently, bronchial biopsies have demonstrated a preponderance of natural killer CD4+ T lymphocytes that express high levels of IL-4. Regulatory T cells play an important role in determining the expression of other T cells, and there is evidence for a reduction in a certain subset of regulatory T cells (CD4+CD25+) in asthma that is associated with increased T_H2 cells. Recently, innate T cells (ILC2) without T cell receptors have been identified that release T_H2 cytokines and are regulated by epithelial cytokines, such as IL-25 and IL-33.

STRUCTURAL CELLS Structural cells of the airways, including epithelial cells, fibroblasts, and airway smooth-muscle cells, are also important sources of inflammatory mediators, such as cytokines and lipid mediators, in asthma. Indeed, because structural cells far outnumber inflammatory cells, they may become the major sources of mediators driving chronic inflammation in asthmatic airways. In addition, epithelial cells may have key roles in translating inhaled environmental signals into an airway inflammatory response and are probably major target cells for ICS.

Inflammatory Mediators Multiple inflammatory mediators have been implicated in asthma, and they may have a variety of effects on the airways that account for the pathologic features of asthma (Fig. 309-4). Mediators such as histamine, prostaglandin D_2, and cysteinyl-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 not yet clear. Although the multiplicity of mediators makes it unlikely that preventing the synthesis or action of a single mediator will have a major impact in clinical asthma, recent clinical studies with antileukotrienes suggest that cysteinyl-leukotrienes have clinically important effects.

CYTOKINES Multiple cytokines regulate the chronic inflammation of asthma. The T_H2 cytokines IL-4, IL-5, and IL-13 mediate allergic inflammation, whereas proinflammatory cytokines, such as TNF-α and IL-1β, amplify the inflammatory response and play a role in more

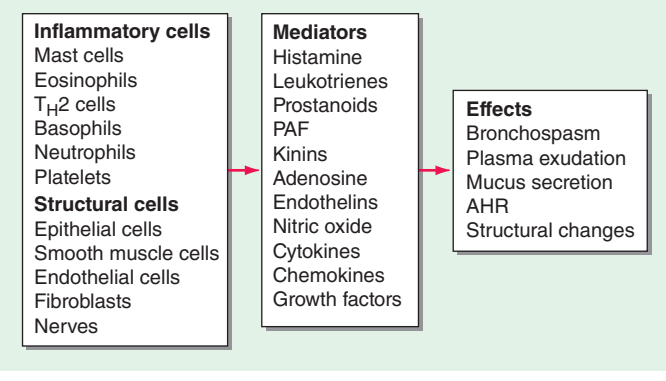

FIGURE 309-4 **Many cells and mediators are involved in asthma** and lead to several effects on the airways. AHR, airway hyperresponsiveness; PAF, platelet-activating factor.