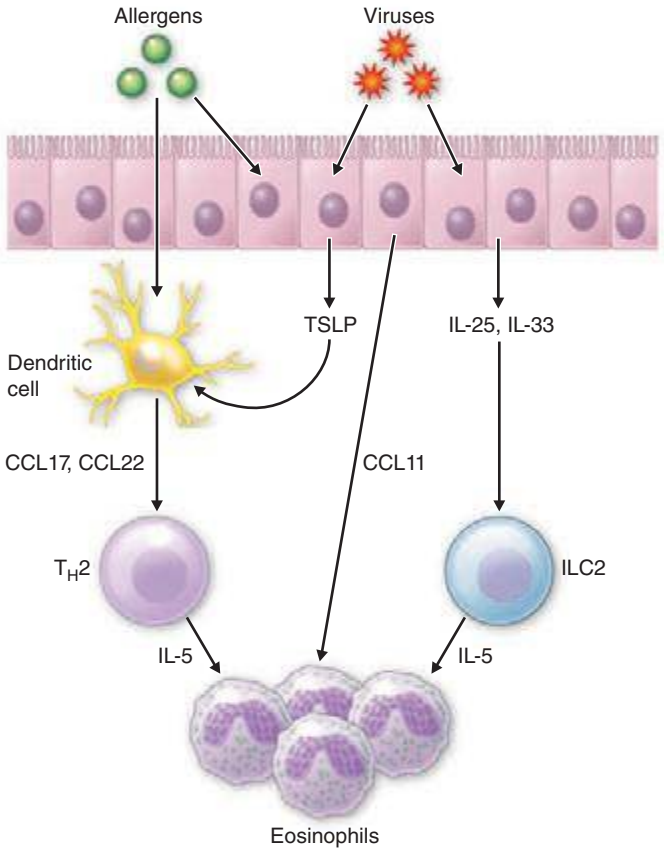

FIGURE 309-5 T lymphocytes in asthma. Allergen interacts with dendritic cells and releases thymus stimulated lymphopoeitin (TSLP), which stimulates activated dendritic cells to release the chemokines CCL17 and CCL22, which attract T helper 2 (T_H2) lymphocytes. Allergens and viral infection may release interleukin (IL)-25 and -33, which recruit and activate type 2 innate lymphoid cells (ILC2). Both T_H2 and ILC2 cells release IL-5 and epithelial cells release CCL11 (eotaxin), which together lead to recruitment of eosinophils into the airways.

severe disease. TSLP is an upstream cytokine released from epithelial cells of asthmatics that orchestrates the release of chemokines that selectively attract T_H2 cells. Some cytokines such as IL-10 and IL-12 are anti-inflammatory and may be deficient in asthma.

CHEMOKINES Chemokines are involved in attracting inflammatory cells from the bronchial circulation into the airways. Eotaxin (CCL11) is selectively attractant to eosinophils via CCR3 and is expressed by epithelial cells of asthmatics, whereas CCL17 (TARC) and CCL22 (MDC) from epithelial cells attract T_H2 cells via CCR4 **(Fig. 309-5)**.

OXIDATIVE STRESS Activated inflammatory cells such as macrophages and eosinophils produce reactive oxygen species. Evidence for increased oxidative stress in asthma is provided by the increased concentrations of 8-isoprostane (a product of oxidized arachidonic acid) in exhaled breath condensates and increased ethane (a product of lipid peroxidation) in the expired air of asthmatic patients. Increased oxidative stress is related to disease severity, may amplify the inflammatory response, and may reduce responsiveness to corticosteroids.

NITRIC OXIDE Nitric oxide (NO) is produced by NO synthases in several cells in the airway, particularly airway epithelial cells and macrophages. The level of NO in the expired air of patients with asthma is higher than normal and is related to the eosinophilic inflammation. Increased NO may contribute to the bronchial vasodilation observed in asthma. Fractional exhaled NO (F_ENO) is increasingly used in the diagnosis and monitoring of asthmatic inflammation, although it is not yet used routinely in clinical practice.

TRANSCRIPTION FACTORS Proinflammatory transcription factors, such as nuclear factor-κB (NF-κB) and activator protein-1, are activated in asthmatic airways and orchestrate the expression of multiple inflammatory genes. More specific transcription factors that are involved include nuclear factor of activated T cells and GATA-3, which regulate the expression of T_H2 cytokines in T cells.

Effects of Inflammation The chronic inflammatory response has several effects on the target cells of the airways, resulting in the characteristic pathophysiologic and remodeling changes associated with asthma. Asthma may be regarded as a disease with continuous inflammation and repair proceeding simultaneously, although the relationship between chronic inflammatory processes and asthma symptoms is often obscure.

AIRWAY EPITHELIUM Airway epithelial shedding may be important in contributing to AHR and may explain how several mechanisms, such as ozone exposure, virus infections, chemical sensitizers, and allergens (usually proteases), can lead to its development, as all of these stimuli may lead to epithelial disruption. Epithelial damage may contribute to AHR in a number of ways, including loss of its barrier function to allow penetration of allergens; loss of enzymes (such as neutral endopeptidase) that degrade certain peptide inflammatory mediators; loss of a relaxant factor (so called epithelial-derived relaxant factor); and exposure of sensory nerves, which may lead to reflex neural effects on the airway.

FIBROSIS In all asthmatic patients, the basement membrane is apparently thickened due to subepithelial fibrosis with deposition of types III and V collagen below the true basement membrane and is associated with eosinophil infiltration, presumably through the release of profibrotic mediators such as transforming growth factor-β. Mechanical manipulations can alter the phenotype of airway epithelial cells in a profibrotic fashion. In more severe patients, there is also fibrosis within the airway wall, which may contribute to irreversible narrowing of the airways.

AIRWAY SMOOTH MUSCLE In vitro airway smooth muscle from asthmatic patients usually shows no increased responsiveness to constrictors. Reduced responsiveness to β-agonists has also been reported in postmortem or surgically removed bronchi from asthmatics, although the number of β-receptors is not reduced, suggesting that β-receptors have been uncoupled. These abnormalities of airway smooth muscle may be secondary to the chronic inflammatory process. Inflammatory mediators may modulate the ion channels that serve to regulate the resting membrane potential of airway smooth-muscle cells, thus altering the level of excitability of these cells. In asthmatic airways there is also a characteristic hypertrophy and hyperplasia of airway smooth muscle, which is presumably the result of stimulation of airway smooth-muscle cells by various growth factors such as platelet-derived growth factor (PDGF) or endothelin-1 released from inflammatory or epithelial cells.

VASCULAR RESPONSES There is increased airway mucosal blood flow in asthma, which may contribute to airway narrowing. There is an increase in the number of blood vessels in asthmatic airways as a result of angiogenesis in response to growth factors, particularly vascular endothelial growth factor. Microvascular leakage from postcapillary venules in response to inflammatory mediators is observed in asthma, resulting in airway edema and plasma exudation into the airway lumen.

MUCUS HYPERSECRETION Increased mucus secretion contributes to the viscid mucous plugs that occlude asthmatic airways, particularly in fatal asthma. There is hyperplasia of submucosal glands that are confined to large airways and of increased numbers of epithelial goblet cells. IL-13 induces mucus hypersecretion in experimental models of asthma.

NEURAL REGULATION Various defects in autonomic neural control may contribute to AHR in asthma, but these are likely to be secondary to the disease, rather than primary defects. Cholinergic pathways, through the release of acetylcholine acting on muscarinic receptors, cause bronchoconstriction and may be activated reflexly in asthma.