

Inflammatory Disorders Associated with Allergy



Overview of Immunopathogenesis and Implications for Treatment

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KEYWORDS

- Cytokine • Eosinophil • Atopic dermatitis • Chronic rhinosinusitis • Nasal polyp
- Asthma • Monoclonal antibody

KEY POINTS

- Over the past 2 decades, the pathogenesis of chronic inflammatory conditions associated with allergy has been increasingly characterized.
- A large number of T-cell subsets have been identified that appear to play active roles in coordinating the pathologic responses in atopic dermatitis, chronic rhinosinusitis, and asthma.
- With the improved understanding of potential molecular targets in these diseases, it is now possible to provide specific therapies that block relevant cytokines.

INTRODUCTION

Over the past 2 decades, we have witnessed consistent increases in the prevalence of chronic inflammatory diseases that are associated with immunoglobulin (Ig)E-mediated immunologic hypersensitivity. During this same period, there have been major advances in our understanding of the natural history and pathogenesis of these diseases. Innovative use of mouse experiments has helped uncover the presence of new T-cell subtypes and cytokines and the development of relevant knockout models has been essential in characterizing the functionality of these cells and proteins. Subsequent studies in humans have sought to determine the relevance of these cells to specific forms of allergic disease. In addition to these developments, a great deal has been learned about the clinical and pathogenetic heterogeneity of atopic diseases. Large-scale epidemiologic studies have revealed that there are distinct phenotypes that are characterized by differences in both clinical (eg, age of onset, severity

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level, medication responsiveness, specific IgE, and eosinophils in body fluids) and molecular (eg, cytokines, chemokines, and protein products) profiles. In this review, the pathogenesis of atopic dermatitis, chronic rhinosinusitis with nasal polyposis, and asthma is considered, with a special emphasis on relevant inflammatory cells and molecules that might ultimately serve as therapeutic targets.

ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by skin dryness, pruritis, erythema, papule formation, and lichenification. It most often begins in early childhood but occasionally starts during the adult years. It is usually the first of the chronic allergy-associated inflammatory diseases to be expressed. It is associated with elevated serum IgE and often occurs with other atopic diseases, including asthma, rhinitis, and food allergy. There are a number of important factors that contribute to the symptoms of AD, including alterations of the skin barrier, abnormalities in innate immune function, alterations of microbial colonization of skin, and increases in Th2 adaptive immune responses. However, despite the tremendous progress made in the characterization of the pathology and molecular biology of AD, many aspects of its pathogenesis remain poorly understood (Fig. 1).

Skin Barrier Function

The main function of the skin is to form a physical barrier against external insults. In patients with AD, there is a significant degree of barrier dysfunction that is central to the disease. Among the causes of altered barrier function, many patients have been

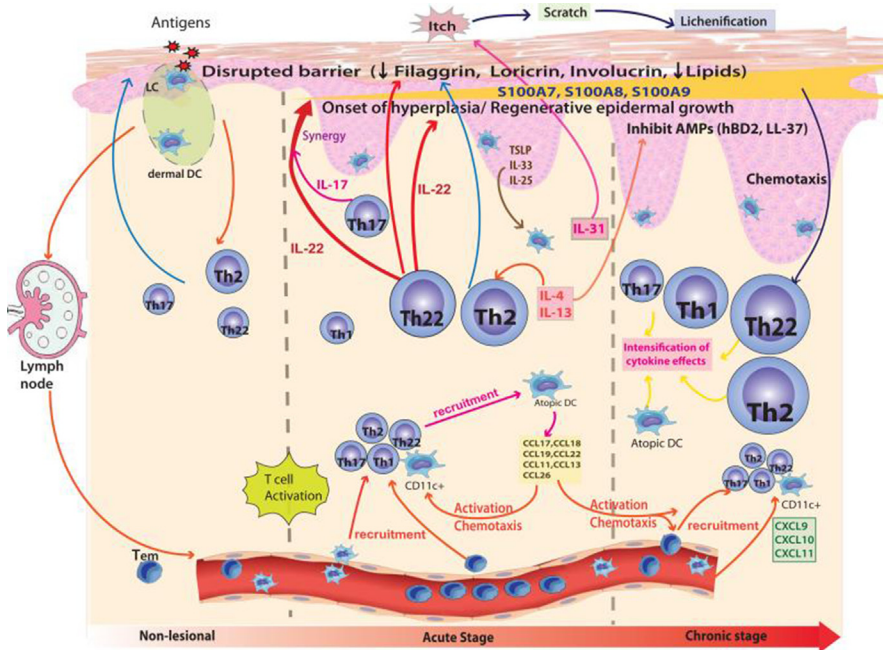


Fig. 1. Immunologic pathways involved in different phases of AD. (From Gittler J, Shemer A, Suárez-Farinas M, et al. Progressive activation of T(H)2/T(H) 22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol* 2012;130:1344–54; with permission.)

identified with a defect in the expression of the filaggrin (*FLG*) gene.¹ *FLG* is responsible for cross-linkage of keratin filaments into tight bundles and moisturization of the stratum corneum, both of which are key elements in skin integrity.¹ Studies have demonstrated a strong link between the incidence of AD and loss-of-function variants in the *FLG* gene²; up to 50% of patients with AD carry *FLG* mutations. In addition, patients with AD have a significant reduction in skin ceramides, which are lipids that contribute to the regulation of water retention in the stratum corneum.³ Patients with AD have a marked reduction of ceramides in both lesional and nonlesional skin compared with healthy individuals. Finally, there appears to be an overactivation of epidermal proteases in the skin of patients with AD. These defects are induced both by genetic variants as well as direct effects of inflammation on those proteases. This disruption of the skin barrier allows for an enhanced penetration of biologic and chemical agents through the epidermis and dermis and elicitation of immunologic activation which may cause skin inflammation.

Inflammation

Dendritic cells

Dendritic cells (DCs) play an important role in the early events of AD. Once foreign antigens have penetrated through the epidermis, they are taken up by cutaneous DCs (Langerhans cells and infiltrating inflammatory dendritic epidermal cells) and processed for presentation. Following contact with these antigens, the DCs migrate to draining lymph nodes, where they present antigens to naive T cells and then direct T-cell differentiation. During this process, thymic stromal lymphopoietin (TSLP) is released by keratinocytes, which promotes T-helper 2 (Th2) inflammation.

T cells

In the acute lesions of AD, Th2 and Th22 cells have been shown to be the predominant cell types, whereas there are lesser number of Th17 cells.⁴ Cytokines produced by Th2 cells (interleukin [IL]-4, IL-13, and IL-31) and Th22 cells (IL-22) have been shown to suppress *FLG* and loricrin, which are critical to skin integrity^{5,6}; however, this effect is observed in acute lesional skin as well as noninvolved skin of patients with AD, implying that these changes are not responsible for disease activity. IL-4 and IL-13 also regulate the class-switching of B-cell production of IgM to IgE, which is a hallmark of AD. In addition, IL-4 alone plays an important role in the maturation of naive T cells to Th2 cells. Th2-derived IL-31 has been shown to induce several chemokine genes that are associated with atopic skin inflammation, such as CCL1, CCL17 (TARC), and CCL22, which promotes ongoing skin inflammation. In addition, IL-31 appears to play a critical role in the induction of pruritus, potentially by directly stimulating nerve receptors in the skin.⁷ IL-22 is produced by a unique T-cell subset, and its release is associated with marked activation of an epidermal differentiation complex (EDC) gene cluster, leading to large increases in the expression of EDC S100 proteins and subsequent increases in chemotaxis of T cells, monocytes, and neutrophils.⁸ IL-17, secreted from Th17 cells, has been shown to enhance the production of IL-6 and IL-8 from keratinocytes,⁹ which induce neutrophil infiltration of skin and modulates fibroblast function.¹⁰ IL-17 also has been shown to positively affect host resistance to cutaneous infections, including cutaneous antimicrobial proteins. Given both the beneficial and deleterious effects of IL-17 in AD, it is unclear what net effect IL-17 has on AD lesions.

As AD lesions enter the chronic phase, IL-13, IL-31, and IL-22 release is intensified, whereas the release of IL-4 is diminished.⁴ IL-17 release is present but to a lesser extent than in acute lesions. In addition, there appears to be activation of Th1 cells

and their cytokines (eg, interferon gamma), which may be either primarily involved in pathogenesis or might be acting as a counterregulatory mechanism of the Th2 pathway. Overall, these observations suggest that maintenance of chronic AD lesions are associated with a mixed cellular response, most prominently Th2 and Th22 and to a much lesser extent Th1 and Th17.

Innate lymphoid cells

Innate lymphoid cells (ILCs) have recently been shown to play an important role in skin lesions of AD, and this effect may be most important early in the course of the disease before the arrival of antigen-specific Th2 cells. Key features of ILC2 cells include development from a common lymphoid progenitor in response to IL-7 and IL-33; lack of antigen-specific receptors; and dependence on the transcription factors GATA-3 and ROR-alpha. Like Th2 cells, ILC2 cells are a rich source of IL-5 and IL-13, but usually not IL-4. In the lesional skin of patients with AD, ILC2s are highly enriched.¹¹ Their function is thought to be largely regulated by keratinocyte-derived cytokines, such as IL-25 (IL-17E), IL-33, and TSLP in response to epithelial injury.

Regulatory T cells

Regulatory T cells (Tregs) are another potentially important modulator of skin immune responses. Tregs have been shown to be increased in the peripheral blood¹² but not in the skin lesions of patients with AD.¹³ One interesting notion is that Tregs in patients with AD appear to decrease their immunosuppressive activity when they are activated by superantigens from *Staphylococcus aureus*.¹⁴ This observation may contribute to *S aureus*-mediated augmentation of skin inflammation in patients with AD.

Mast cells

Mast cells express the high-affinity IgE receptor (FcεRI) and release a wide variety of proinflammatory mediators on activation. Increased mast cell numbers and activation were reported in the chronic skin lesion of AD.¹⁵ Although they are generally considered effector cells of skin inflammation, immunosuppressive roles of mast cells also have been demonstrated in mouse AD models.

Eosinophils

Although blood and tissue eosinophilia is often observed in patients with AD, the role of eosinophils in the pathogenesis of AD has not been clearly established. During periods of increased symptoms, patients with AD demonstrate increased serum concentrations of IL-5 and eosinophil chemoattractants, such as eotaxin.¹⁶ However, it is not clear that eosinophils are responsible for either the skin lesions or itching characteristic of AD.

Potential Immunologic Treatments

The foregoing discussion indicates that there are a number of molecular targets that are relevant to atopic dermatitis, and the inhibition of which may reduce the symptoms of AD. Clinical trials have demonstrated that antagonism of IL-4 and IL-13 by blocking the alpha subunit of the IL-4 receptor (dupilumab) results in significant reductions in disease activity.¹⁷ It remains to be seen whether isolated inhibition of IL-13 using an anti-IL-13 antibody will have the same degree of benefit. IL-5 blockade, with attendant reductions in blood and tissue eosinophilia, did not consistently affect the signs or symptoms of AD.¹⁸ Other molecules that will be prime candidates for drug intervention include IL-17, IL-22, IL-31, TSLP, IL-25, and IL-33.

CHRONIC RHINOSINUSITIS WITH NASAL POLYPOSIS

Chronic rhinosinusitis (CRS) is a disease with persistent or recurrent symptoms that involves the mucosa of the nose and paranasal sinuses. The presence of nasal polyps (NPs), which represent hyperplastic evaginations of sinus mucosa into the nasal passages and are present in up to one-third of patients with CRS, increases the burden of disease and the likelihood of symptom persistence after therapy. The etiology of CRS is complex and related to an interplay of genetics and environmental exposures, including allergens and microbial species (Fig. 2).

Mucociliary Clearance

In healthy nasal and sinus tissue, the epithelium is the body's first line of defense against inhaled noxious substances and is responsible for protecting the upper airway from infiltration by pathogens, such as viruses, bacteria, and fungi, toxic or irritating substances, and potential allergens. Respiratory epithelial cells are interconnected by tight junctions to form a protective physical barrier against these substances. Once in contact with the epithelium, particulate matter is trapped by airway mucus and then removed by movement of the mucociliary blanket. A large list of pathogens has been shown to produce compounds that impair ciliary motion, including

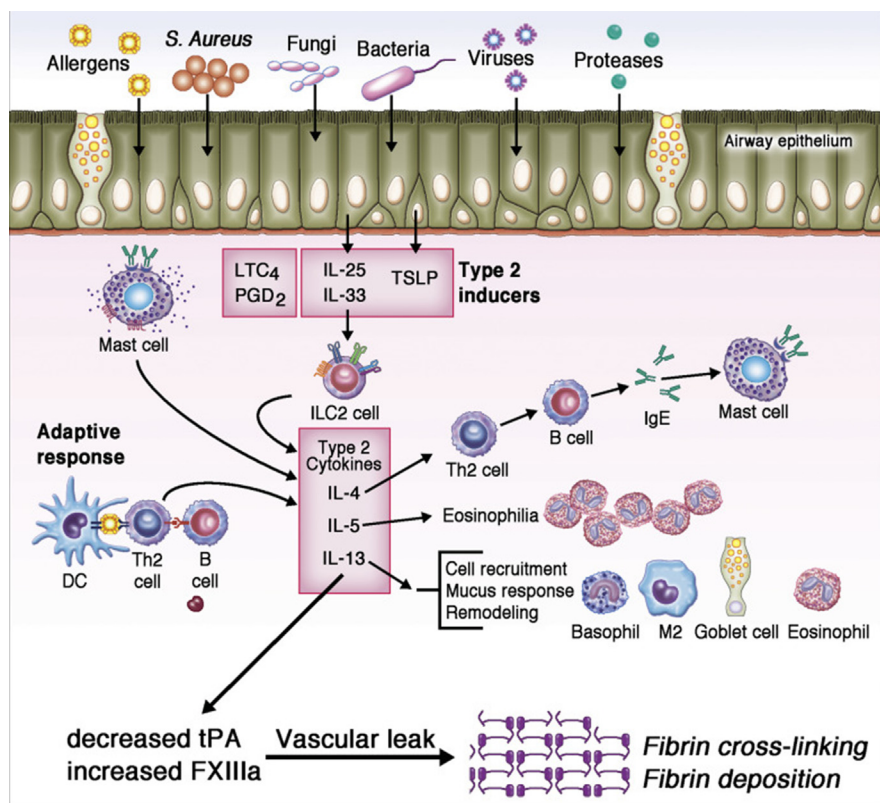


Fig. 2. Role of the host immune response in patients with CRSwNP. (From Stevens WW, Lee RJ, Schleimer RP, et al. Chronic rhinosinusitis pathogenesis. *J Allergy Clin Immunol* 2015;136(6):1448; with permission.)

Haemophilus influenzae, *Staphylococcus pneumoniae*, *S aureus*, *Aspergillus fumigatus*, and *Pseudomonas aeruginosa*¹⁹ Sinus ostial obstruction caused by mucosal swelling or secretions, with subsequent sinus cavity hypoxia, also can reduce mucociliary transport.²⁰

Host Defense and Inflammation

Epithelium

In addition to the production and transportation of mucus, the nasal-sinus epithelium produces a large number of antimicrobial compounds, such as lysozyme, lactoferrin, antitrypsin, defensins, *S100 proteins*, and surfactants.²¹ Regulation of these substances occurs through Toll-like receptors (TLRs) that recognize microbial pathogen-associated molecular patterns and then stimulate the secretion of defense molecules, within a few hours of contact with microbes. In addition to TLRs, epithelial cells also express taste family type 2 receptor bitter taste receptors.²² These receptors are able to detect specific molecules secreted by bacteria, which leads to very rapid increases in ciliary movement and generation of defense molecules.²²

In addition to barrier functions and the elicitation of innate defensive molecules, epithelial cells also can release various inflammatory mediators, most notably TSLP, which acts on dendritic cells to promote the generation of Th2 cells from naïve T cells.²³ In addition, TSLP acts to augment the release of type 2 cytokines (IL-4, IL-5, and IL-13) from Th2 cells, as well as innate immune cells, such as ILC2 cells. There is also evidence of IL-25 and IL-33 activity in CRS with NP (CRSwNP) tissue, although much of the data are conflicting.²³ In nasal and sinus mucosa, IL-4 and IL-13 contribute to eosinophilic inflammation (via effects on eotaxins), whereas IL-5 is the key factor that regulates the release of eosinophil progenitors from the bone marrow, eosinophil activation, and eosinophil survival.

Innate lymphoid cells

Other mechanisms of innate immunity appear to be important in chronic sinusitis and NPs. ICS2 have been shown to be increased in NPs. ILC2 cells may be important early in CRSwNP following an initial event that induces epithelial damage. Following epithelial binding and activation, TSLP may be released, leading to activation of ILC2 cells and secretion of IL-5 and IL-13.²⁴ This local signal from ILC2 cells in the nasal and sinus tissue leads to eosinopoiesis and eosinophil ingress into the upper airway. Large numbers of mast cells and basophils also are present in patients with CRSwNP compared with healthy controls.²⁵ Eosinophils, mast cells, and basophils have typically been identified in the mucosa of Western patients with CRSwNP but not in individuals of Asian descent.²⁶ These cell types release a variety of basic proteins (eg, eosinophil cationic protein) and inflammatory mediators (lipid-derived mediators, cytokines, and chemokines) that lead to chronic mucosal injury and may help perpetuate ongoing inflammation. These inflammatory signals have been explored to a much greater extent in asthma, and are discussed at length in a later portion of this article.

T cells and B cells

Once inflammation has been induced, in part due to persistent exposure to an exogenous stimulus, such as a microbe or allergen, the adaptive immune response may come into play. NP tissue has consistently demonstrated increases in CD4+ T cells as compared with healthy nasal and sinus tissue.²⁷ B cells, including plasma cells, also have been shown to be increased in polyp tissue, along with multiple antibody isotypes, including IgG1, IgG2, IgG3, IgG4, IgA, IgM, and IgE.²⁸ For the most part, the targeted antigen for these antibodies is not known; however, a small subset of patients with CRSwNP who are colonized with *S aureus* have detectable specific IgE

antibodies directed against *S aureus* enterotoxins.²⁹ Enterotoxins act as superantigens and broadly activate T lymphocytes, potentially increasing the inflammatory infiltrate into the local sinus tissue.

Tissue remodeling

In addition to the inflammation noted previously, NP tissue in CRSwNP shows the formation of pseudocysts and stromal edema but shows none of the fibrosis or basement membrane thickening that is seen in patients with CRS without NPs. The edema appears to be due to vascular leakage with extravasation of plasma proteins through the epithelial barrier. Recent studies have revealed that this phenomenon may, in part, be due to products of the clotting cascade, including fibrin and other factors.³⁰

Potential Immunologic Treatments

One small trial of ant-IgE therapy (omalizumab) in patients with CRSwNP and anti-*Staphylococcus aureus* enterotoxin A IgE reported significant improvement in polyp symptoms and size.³¹ Abrogation of tissue eosinophils using an anti-IL5 antibody is another plausible approach, and one small trial yielded positive results on polyp reduction in a subset of patients.³² Most recently, an antibody to the IL-4 receptor alpha chain (dupilumab), blocking both IL-4 and IL-13, demonstrated significant improvement in CRSwNP.³³ Other targets that are currently being considered include TSLP and possibly IL-25 and IL-33.

ASTHMA

Asthma is a chronic airway disease characterized clinically by episodic chest symptoms related to airways obstruction and hyperresponsiveness. For many years, it has been recognized that asthma is a heterogeneous condition, both clinically and pathogenetically. One of the principal paradigms for dividing asthma into phenotypes has been based on the presence or absence of eosinophils. These differences between asthma subtypes will be highlighted in this brief review of asthma pathogenesis (Fig. 3).

Inflammation

Epithelial cells

Epithelial cells in the lower airways are largely responsible for mucociliary clearance of inhaled foreign material. As in the nose and sinuses, epithelial cells in the lungs are also capable of binding to inhaled substances via pattern recognition receptors, such as TLRs, leading to activation of the epithelium with subsequent generation of cytokines. TSLP, IL-25, and IL-33 have all been shown to be significantly increased in patients with asthma.³⁴ Two important functions of these epithelial-derived cytokines include polarization of dendritic cell function, leading to a shift toward Th2 cell development, along with an increase in cytokine release from Th2 cells and other effector cells. In ongoing disease, epithelial cells continue to drive airway inflammation by producing chemokines and cytokines that activate eosinophils, neutrophils, and other cells of the innate immune system.

Th2 cells

Pathologic studies have demonstrated that CD4+ T cells are present in increased numbers in most patients with asthma, along with elevations of the Th2 cytokines IL-4, IL-5, and IL-13.³⁵ In lung tissue, IL-4 and IL-13 have critical effects on most airway structures, leading to many of the pathologic hallmarks of asthma: eosinophilic inflammation (via effects of eotaxins), increased goblet cell maturation and mucus

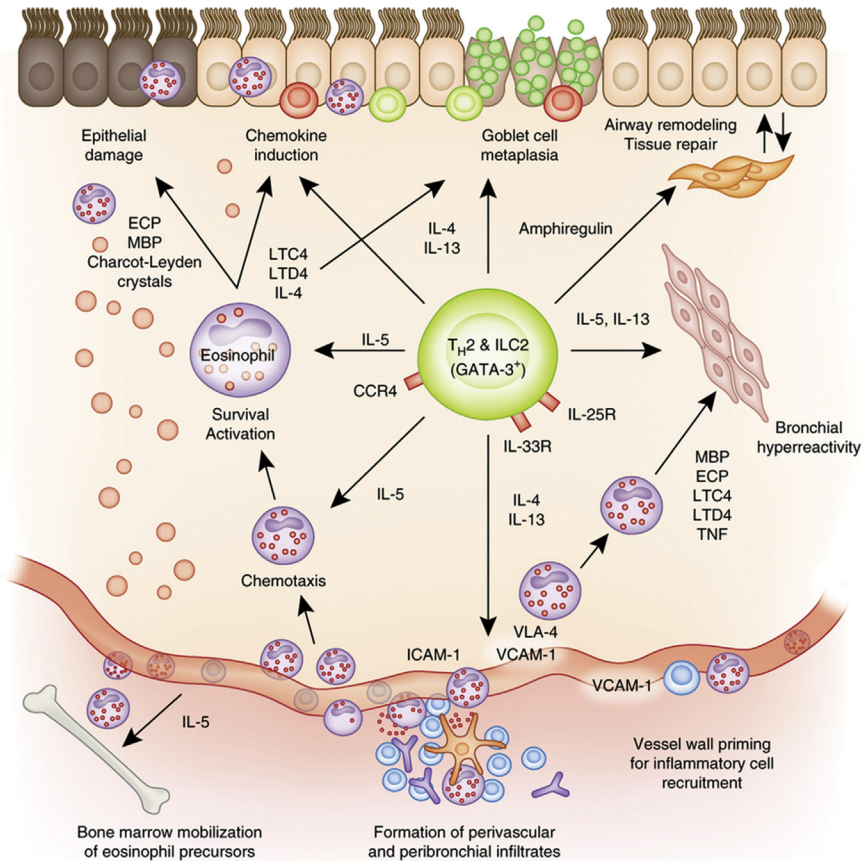


Fig. 3. Overview of functions of Th2 cells and ILC2 cells in asthma. ECP, eosinophil cationic protein; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; VLA, very large antigen. (From Lambrecht BN, Hammad H. The immunology of asthma. *Nat Immunol* 2015;16:46; with permission.)

secretion, enhanced development of fibroblasts, increased collagen synthesis (which is incorporated into the basement membrane), and alterations in bronchial smooth muscle responsiveness to beta-adrenergic agonists.³⁶ The most important immunologic effect of both IL-4 and IL-13 is the induction of switching from IgM to IgE production in B cells. IL-4, but not IL-13, also promotes the development of naive T cells into Th2 cells, a potentially important effect that leads to persistent Th2 infiltration of airway tissue.³⁶

Th17 cells

Th17 cells represent a separate subset of CD4⁺ cells that are capable of releasing IL-17 as their principal cytokine product. Development of these cells from naive T-cell precursors is not completely understood, but appears to rely on IL-6, IL-23, and transforming growth factor (TGF)-beta.³⁷ IL-17 is a key member of the IL-17 family of cytokines (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E [IL-25], and IL-17F). The primary identified function of IL-17A is to promote inflammation through induction of macrophage and neutrophil chemokines and growth factors

including CXCL1, CXCL2 (macrophage inflammatory protein-2), CXCL5, CXCL8 (IL-8), CXCL9, CXCL10, CCL-2 (monocyte chemoattractant protein [MCP-1]), granulocyte colony-stimulating factor (CSF), and granulocyte macrophage CSF (GM-CSF).³⁸ There is growing evidence that Th17 cells and IL-17 are involved in human asthma. IL-17 A⁺ cells along with IL-17 and other Th17 cytokines increase in the blood of individuals with asthma and appear to be correlated with the degree of severity of asthma.³⁹ In addition, both IL-17A and IL-8 mRNAs have been shown to be significantly increased in sputum of individuals with asthma compared with controls, and sputum IL-17A and IL-8 mRNA are more likely to be elevated in patients with more severe asthma.⁴⁰ More recently, increased numbers of IL-17A⁺CD4⁺ cells have been shown to be present in the tissue of individuals with asthma.⁴¹ Although initial hypotheses predicted that the presence of Th17 cells would be associated with increased airway neutrophils, a recent investigation demonstrated that patients with elevated numbers of Th17 cells also have elevated numbers of airway eosinophils and there were no correlations between markers of a Th17 molecular phenotype and blood, sputum, or airway tissue neutrophils.⁴² It may be that the activity of airway neutrophils may be more relevant to asthma severity than their number.

Th9 cells

Th9 cells have been identified as a distinct helper T-cell subset that produces IL-9, IL-10, and IL-21.⁴³ IL-9 is a mast cell growth factor that promotes IL-4-driven antibody production by B cells and can also induce goblet cell metaplasia. In a knockout mouse model of allergic airway disease, IL-9 can reproduce all of the cardinal features of asthma.⁴⁴ IL-9 has high expression in the lungs of patients with allergic asthma following segmental allergen challenge,⁴⁵ however.

Innate lymphoid cell 2

Valuable information regarding the etiology of eosinophilic airway inflammation came from a recombination-activating gene recombinase knockout mouse model of asthma, in which inhalation of allergen led to bronchial eosinophilia in the complete absence of mature T and B cells.⁴⁶ These findings suggested the possibility of generating a Th2 cytokinelike profile and eosinophilia without Th2 cells. As noted previously, inhalation of an exogenous antigen, particularly those that consist of or contain a protease (eg, house dust mite) may directly induce epithelial injury, leading to epithelial IL-33 release, activation of ILC2 cells, and finally generation of IL-5 and IL-13.⁴⁶ An alternative route of ILC2 activation has been attributed to leukotriene D4 (LTD4), which has been shown to be released following a single exposure to a proteolytic allergen.⁴⁷ ILC2 cells also have been shown to express major histocompatibility complex class II and costimulatory molecules, indicating that they may act as antigen-presenting cells that activate CD4⁺ T cells. In addition to their role in allergy, mouse models have demonstrated that ILC2 cells may lead to viral-induced increases in airway eosinophils and other markers of airway inflammation.⁴⁸ Although the precise signals for ILC2 recruitment are not yet fully understood, there is evidence that the receptor for prostaglandin D2 (CRTH2), for LTD4 (CysLTR1), and chemokines (CCR4 and CCR8) may be involved.⁴⁹

Eosinophils

Approximately 50% of patients with severe asthma have evidence of airway eosinophilia. These cells, which are drawn into the systemic circulation by IL-5, make their way into the lung vasculature and then enter the airway tissue under the influence of eotaxins. Once in the tissue, eosinophils release their granule proteins, including

eosinophil cationic protein, major basic protein (MBP), eosinophil peroxidase, and eosinophil-derived neurotoxin, which are directly toxic to epithelial and other airway structures.⁵⁰ In addition, MBP has been shown to stimulate leukotriene C4 (LTC4) release from basophils, which may have clinical importance. Eosinophils also can synthesize and release a large number of proinflammatory cytokines, including IL-4, IL-5, IL-13, IL-25, GM-CSF, and IL-8, and chemokines, including RANTES (Regulated on Activation, Normal T-Cell Expressed and Secreted) and eotaxin.⁵¹ Overall, these eosinophil-derived products augment eosinophilic inflammation in the airway and may also promote neutrophil recruitment. Important cell surface markers on eosinophils include the IL-5 receptor, CCR3 (receptor for eotaxins), CRTH2, and Siglec-8. Siglec-8 engagement on eosinophils results in apoptosis, suggesting that this receptor may play an important role in the regulation of eosinophil accumulation and survival.⁵² Eosinophils have been shown to be significantly increased in patients with severe, exacerbation-prone asthma compared with individuals with mild-moderate disease, and may negatively affect lung function.⁵³

Mast cells

There is strong evidence that mast cells play an important role in the early asthmatic reaction following allergen exposure with an increase in histamine, prostaglandin D₂ (PGD₂) and LTC4. Mast cells also synthesize and release a vast array of proinflammatory cytokines (eg, IL-4, IL-5, IL-6, IL-13, tumor necrosis factor [TNF]-alpha) and chemokines (RANTES, MCP-1, CXCL8) that act to recruit inflammatory cells, such as eosinophils, activated macrophages, and lymphocytes.⁵⁴ However, in diseases such as asthma, mast cells within the asthmatic airways appear to be present in a chronically activated state with evidence of ongoing mediator secretion. Studies show that bronchoalveolar lavage fluid of patients with stable asthma has increased numbers of mast cells⁵⁵ and increased levels of the mast cell mediators histamine and tryptase, suggesting ongoing activation and degranulation.⁵⁵

Airway remodeling

It has been hypothesized that chronic airway inflammation, tissue injury, and abnormal repair mechanisms lead to structural changes in the airway walls of individuals with asthma, which may lead to irreversible (or partially reversible) airflow obstruction. Pathologic characteristics of remodeling, which include goblet cell hyperplasia, subepithelial fibrosis, increased airway smooth muscle mass, and bronchial hypervascularity, have all been carefully studied in small numbers of patients and possible molecular mechanisms have been identified.⁵⁶ IL-13 may be the most instrumental of the type 2 cytokines, and plays a key role in many of these processes, particularly goblet cell hyperplasia and subepithelial fibrosis.⁵⁷ Other mediators of remodeling include vascular endothelial growth factor, which is important in neovascularization⁵⁸; TGF-beta, which contributes to fibrosis and increased airway smooth muscle⁵⁹; and tissue inhibitor of metalloproteinase-1, which acts as an important profibrotic factor in fibrosis.⁶⁰ A complex interplay of these and other factors makes the treatment of airway remodeling a challenge to physicians who treat asthma.

Potential Immunologic Treatments

In type-2 (eosinophilic) asthma, IL-5 and IL-4/-13 have been considered critical cytokines in both the development and persistence of asthma. Monoclonal antibodies directed against IL-5 or its receptor (mepolizumab, reslizumab, benralizumab) have demonstrated significant reductions in asthma exacerbations and variable improvements in FEV1 (forced expiratory volume in 1 second) and patient-reported

outcomes.^{61–63} Similarly, antibodies against IL-13 or the IL-4 receptor (lebrikizumab, tralokinumab, dupilumab) also have shown significant improvements in exacerbations,^{64,65} FEV1,^{64–66} and patient-reported outcomes. Efforts to inhibit IL-9 did not result in changes in any clinical parameters of asthma.⁶⁷ Epithelial-derived cytokines, including TSLP, IL-25, and IL-33, are all plausible targets in type-2 asthma, and a proof-of-concept study of anti-TSLP (AMG 157) demonstrated robust inhibition of the early and late asthmatic responses to allergen inhalation.⁶⁸ Other potential targets in type-2 asthma include the prostaglandin receptor CRTH2, which has shown variable success in a number of trials with different drugs.⁶⁹ In non-type 2 (low eosinophil) asthma, TH-17 and GM-CSF both represent possible targets, although monoclonal antibodies against these cytokines have not demonstrated efficacy to date, possibly due to patient selection issues.^{70,71}

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