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Pathogenesis of Allergic Airway Inflammation

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Abstract Advances have been made in defining the mechanisms for the control of allergic airway inflammation in response to inhaled antigens. Several genes, including *ADAM33*, *DPP10*, *PHF11*, *GPRA*, *TIM-1*, *PDE4D, OPN3*, and *ORMDL3*, have been implicated in the pathogenesis and susceptibility to atopy and asthma. Growing evidence associates asthma with a systemic propensity for allergic T-helper type 2 cytokines. Disordered coagulation and fibrinolysis also exacerbate asthma symptoms. Balance among functionally distinct dendritic cell subsets contributes to the outcome of T-cell-mediated immunity. Allergen-specific T-regulatory cells play a pivotal role in the development of tolerance to allergens and immune suppression. The major emphasis on immunotherapy for asthma during the past decade has been to direct the immune response to a type 1 response, or immune tolerance. In this review, we discuss the current information on the pathogenesis of allergic airway inflammation and potential immunotherapy, which could be beneficial in the treatment of airway inflammation, allergy, and asthma.

Keywords Allergic airway inflammation · Asthma · Asthma gene · Coagulation system · Cytotoxic T cell · Dendritic cell · Flt3 ligand · KCa3.1 · Matrix metalloproteinase · T helper cell · T regulatory cell

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Introduction

Asthma is a disease of chronic airway inflammation characterized by reversible airway obstruction, airway hyperresponsiveness (AHR), infiltration of eosinophils and T-helper type 2 (Th2) cells into the airway submucosa, mucus hypersecretion, and airway remodeling [1]. Allergic asthma is classified as a type 1 hypersensitivity reaction. This involves allergen-specific immunoglobulins of the IgE class bound to high-affinity Fcε receptors on the surfaces of basophils and mast cells present in the subepithelial layer of the airways. Cross-linking of these bound IgE molecules results in an immediate release of mediators, including leukotrienes, prostaglandins, and histamine, that are capable of contracting airway smooth muscle cells and that induce edema and mucus secretion, leading to narrowed, constricted airways. Locally produced chemokines stimulate the recruitment of eosinophils, macrophages, neutrophils, and T lymphocytes [1]. Once present, effector cells such as eosinophils release a collection of toxic granules that in turn cause prolonged bronchoconstriction and damage epithelial layers. This damage, coupled with profibrotic cytokines also released by eosinophils and epithelial cells may lay the groundwork for airway remodeling to begin [2]. Cytokines released at the time of mast cell degranulation can have more global effects. These include recruiting eosinophils from bone marrow and peripheral sources in addition to encouraging their survival (primarily via interleukin [IL]-5 and granulocyte-macrophage colony-stimulating factor) and the stimulation and continued production of IgE by B cells, as well as the induction of vascular cell adhesion molecule-1 by endothelial cells (IL-4) [1]. Cytokines such as IL-4, IL-5, IL-6, and IL-13 ensure that this cycle of allergic inflammation persists (Table 1). The prevalence of asthma has been increasing steadily for several decades. Although

Table 1 Release of cytokines and other mediators and their effects from various cells involved in allergic airway inflammation

Inflammatory cells infiltrated in the lung	Cytokines/mediators released	Biological effects
Cells that exacerbate inflammation and asthma		
Eosinophils, neutrophils	Oxygen radicals and lipid mediators , cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL -6, IL-10, IL-12, and IL-13; TNF-α; and GM-CSF), chemokines (IL-8, RANTES, and MIP-1α), fibrogenic cytokines (TGF-β, IL-11, IL-17, and IL-25)	Prolonged bronchoconstriction, damaged epithelium, airway remodeling
Basophils, mast cells	Histamine, MBP	Vasculature exudation, increased mucus in the airways
Th2 cells	IL-4, IL-5, IL-9, IL-13	Humoral antibody production, chemotaxis and survival of eosinophils
Th17 cells	IL-6, IL-8, IL-17A, IL-17F, IL-22, IL-26	Neutrophilia, AHR, airway remodeling
Dendritic cells	IL-4, IL-12, GM-CSF	Induction of Th2 cells, suppression of Th1 cells
$CD8^+$ T cells	IL-4, IL-5, IL-9, IL-13	AHR, eosinophilia
Cells that suppress allergic and asthmatic response		
T-regulatory cells	IL-10, TGF-β	Prevention of T-cell expansion
$CD8^+$ T cells	IFN-γ, IL-12	Suppression of allergic immune response
Th1 cells	IL-2, IFN-γ, lymphotoxin (TNF-β)	Enhanced cellular response, suppression of Th2 cells
Plasmacytoid dendritic cells	IL-10, TGF-β	T-cell suppression
Regulatory dendritic cells	IL-12 (LPS, bacterial CpG, CpR oligonucleotides)	Induction of Th1 cells

AHR—airway hyperresponsiveness; CpG—cytosine-phosphorothiolated guanine; CpR—cytosine-phosphorothiolated 2 -dioxy-7-deazaguanosine; GM-CSF—granulocyte-macrophage colony-stimulating factor; IFN—interferon; IL—interleukin; LPS—lipopolysaccharide; MBP—major basic protein; MIP—macrophage inflammatory protein; RANTES—regulated on activation, normal T-cell expressed and secreted; TGF—transforming growth factor; Th —T-helper type cell, TNF—tumor necrosis factor

there is an appreciable genetic component [1], external influences may regulate/influence the immune system by affecting the differentiation and activation of T lymphocytes. Therapeutic approaches targeting intrinsic and extrinsic factors have been under extensive investigation.

Th1/Th2 Polarized Immunity

It is generally accepted that allergic respiratory disease in adults is associated with active T-cell immune responses to inhaled allergens that are skewed toward the Th2 phenotype, which is in contrast to a Th1-skewed immunity in healthy individuals. Th1 cells secrete interferon (IFN)-γ, IL-12, and lymphotoxin (tumor necrosis factor-β), whereas Th2 cells secrete IL-4, IL-5, IL-9, and IL-13 (Fig. 1). Th1 cells enhance cellular immune responses; Th2 cells favor humoral antibody production (IgE), such as allergic asthmatic response. The improved hygiene results in a decreased stimulation of a type 1 response and thus leads to a greater stimulation of type 2 responses and a consequent predisposition to allergic diseases. Unequal apoptosis of Th1 and Th2 effector cells in atopic patients leads to preferential deletion of circulating memory or effector Th1 cells [3], especially the high IFN-γ-producing Th1 cells [4•], which contributes to the skewing of the immune response toward surviving Th2 cells. New effector T-cell lineages were identified recently. Th17 cells, which differentiate from naïve $CD4^+$ T cells under the influence of IL-6/IL-21/IL-23 and transforming growth factor (TGF)-β via signal transducer and activator of transcription 3 (STAT3)-RORγt pathway, are mainly responsible for neutrophilia in allergic asthma (Fig. 1) [5•]. In the presence of IL-4 and TGF-β, Th2 cells can be reprogrammed to a new T-cell lineage expressing IL-9 and IL-10, namely Th9 cells (Fig. 1) [6•].

Transcription Factors Responsible for the Th1/Th2 Dichotomy

The determination of T-helper lineage fates of Th1 or Th2 is accompanied by a differential activation, expression, and

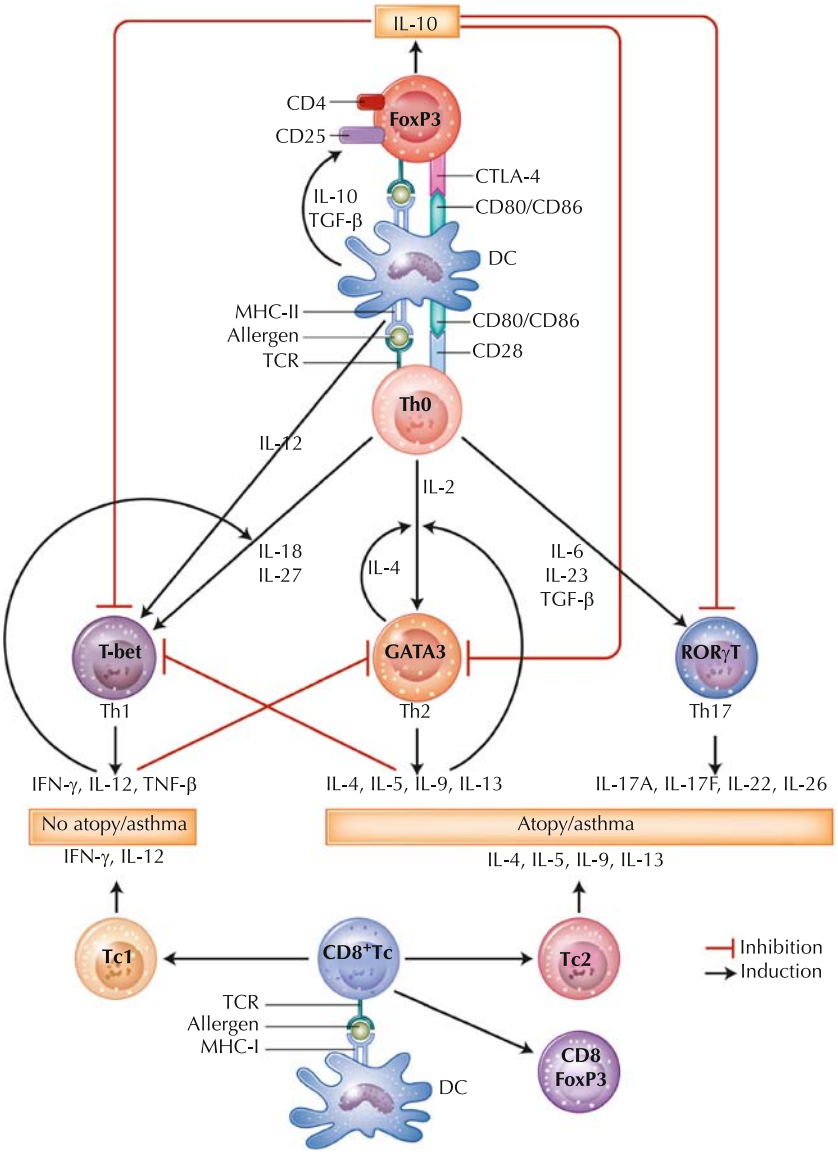

Fig. 1 Differentiation of $CD4^+$ T-helper (Th) cells and $CD8^+$ cytotoxic T cells in allergic asthma. Differentiation of $CD4^+$ Th cells to effector Th1, Th2, or Th17 cells or T–regulatory cells (Tregs) depends on environmental cytokine profile. Cytokines released from Th1 cells can antagonize differentiation and function of Th2 cells and vice versa. Undifferentiated Th0 cells can mature into Th1, Th2, Th17, or Tregs in peripheral lymph organs, depending on the costimulatory signals presented to them, along with antigen, by antigen-loaded dendritic cells (DCs). Functionally, $CD8^+$ effector cytotoxic T cells (Tcs) contain Tc1, Tc2, and $CD8^+FoxP3^+$ regulatory cells. Immunomodulators such as Flt3-ligand or cytosine-phosphorothiolated 2 -dioxy-7-deazaguanosine oligonucleotides may preferentially increase the number of regulatory DCs and/or Tregs inducing Th1 response or T-cell anergy/tolerance to allergen. This could result in the prevention and/or reversal of atopy and/or asthma symptoms. CTLA—cytotoxic T-lymphocyte-associated antigen; FoxP3—forkhead box P3; IFN—interferon; IL—interleukin; MHC—major histocompatibility complex; T-bet—T-box transcription factor; TCR—T-cell receptor; TGF—transforming growth factor; TNF—tumor necrosis factor

functionality of transcription factors in different T-cell lineages, which accordingly induce and suppress lineage-related and non-lineage-related cytokine secretion, respectively. It is becoming evident that cytokines differentially secreted by various dendritic cell (DC) subsets [7, 8, 9••] play an essential role in driving T-cell differentiation (Fig. 1) [7, 8, 9••]. The Th1 master regulator, T-box transcription factor (T-bet), is extensively expressed in polarized Th1 cells, and its expression and activity are induced by IL-12 via STAT4 or by IFN-γ via STAT1 [10]. STAT4 also influences Th1 commitment in a T-bet-independent manner [11]. The transcription factor Runx3 is also upregulated in Th1 cells in a T-bet-dependent manner. T-bet and Runx3 demonstrate a cooperative effect on the production of IFN-γ and silencing of the gene encoding IL-4 in Th1 cells [12]. IL-4 drives differentiation of IL-4-producing Th2 cells through STAT6,

which is necessary and sufficient for the induction of the Th2 master regulator, GATA-3 [13]. GATA-3, through an autocrine pathway, upregulates its own expression in a STAT6-independent manner [14]. Upon T-cell receptor (TCR) stimulation, TCR-inducible transcription factor NFAT1 is also involved in regulating GATA-3 expression [14]. Transcription factor c-Maf is selectively expressed in Th2 cells as a downstream effector of the IL-4/IL-4R/STAT6 signal transduction pathway and primarily regulates IL-4 expression in Th2 cells. The cross-talk between Th1 and Th2 transcription factors is also involved in the regulation of T-cell lineage commitment. STAT6 inhibits the IL-12-STAT4 signaling pathway without involving downstream transcription factor T-bet [15]. In fact, GATA-3 and T-bet target several common genes and exert the opposing effect on their transcription, which consequently influences the choice between Th1 and Th2 lineage commitment [16]. Therefore, both T-bet and GATA-3 work concomitantly with other transcription factors, including nuclear factor of activated T cells, activator protein-1, nuclear factor-κB, and CCAAT/enhancer binding protein b. The counterpart of GATA-3 and T-bet in Th17 cells is RORγt, which is required to activate IL-17 production in Th17 cells and directly/indirectly regulates production of IL-17F and IL-22 in Th17 cells [17].

Lung Dendritic Cells

An emerging concept is that different lung DC subsets induce different immune responses, such as immunity versus tolerance, or Th1 versus Th2. Lung $CD11c^{+}CD11b^{hi}B220^{-}Gr\text{-}1^{-}$ myeloid DCs play a major role in inducing allergic airway inflammation in response to allergen challenge [9••]. $CD11c^{int}Gr\text{-}1^{+}B220^{+}$ DCs identified in mouse lymph nodes produce type 1 IFN and demonstrate tolerogenic potential, which leads to the notion that they are the murine counterpart of human plasmacytoid DCs [18]. De Heer and colleagues [19] demonstrated that lung $CD11c^{int}Gr\text{-}1^{+}B220^{+}$ plasmacytoid DCs suppressed T-cell division and effector T-cell generation induced by myeloid DCs, confirming the involvement of plasmacytoid DCs in regulating lung inflammation. Additionally, IL-10-producing $CD80^{+}CD86^{+}CD40^{+}MHCII^{+}CD8^{-}$ lung DCs induce pulmonary tolerance, which establishes the role of IL-10 in DC biology in conjunction with the fact that IL-10-treated DCs reverse allergic airway inflammation [20].

Lung $CD11c^{high}CD11b^{low}CD103^{+}$ DCs were recently discovered, and their function seems to be related to increased IL-12 production [21], $CD8^{+}$ T-cell stimulation, and particulate antigen uptake [22]. Thus, lung DCs demonstrate a highly flexible phenotype and often serve diverse and opposing functions. We have identified two functionally and phenotypically distinct lung DC subsets, namely $CD11c^{high}CD11b^{low}$ and $CD11c^{low}CD11b^{high}$ in a murine model of allergic airway inflammation [9••]. Under the condition of allergen challenge, the $CD11c^{low}CD11b^{high}$ lung DC subset is rapidly expanded and more prone to induce robust Th2 response as compared with a Th1-prone response induced by $CD11c^{high}CD11b^{low}$ lung DCs [9••]. They also differ in migratory and antigen uptake patterns [23•].

In humans, two subsets of blood DCs—myeloid and plasmacytoid DCs—were identified based on the expression of CD11c, a β_2 integrin. Human blood myeloid DCs are further divided into mDC1 and mDC2, which uniquely express CD1c (BDCA-1) and CD141 (BDCA-3), respectively. Conversely, blood plasmacytoid DCs express CD123 and CD303 (BDCA-2) but not CD11c [24]. The three DC subsets are present in human lung digest and bronchoalveolar lavage fluid (BALF) and can stimulate T-cell proliferation [25]. Functionally, human lung pDCs secret more IFN-α and have lower expression of major histocompatibility complex (MHC) and costimulatory molecules than mDCs [26]. As DCs mature in the lungs, the phenotypic characteristics of lung DCs may not follow the exact same pattern as blood DCs. Possibly as a result, the blood pDC-specific marker CD123 is also expressed on a subpopulation of lung mDCs; this distinction is reflected by a subtle difference in the cytokine/chemokine secretion pattern between $CD123^{+}$ and $CD123^{-}$ lung mDCs [26]. Similar to the murine allergic asthma model, human lung mDCs seem to play a more important role in the induction of asthma, as an enhanced influx of functionally active antigen-presenting mDCs into the respiratory tract is observed following endotoxin administration [27•]. However, another study involving humans that analyzed BALF DCs suggested that both pDCs and mDCs are recruited into the lungs in asthma patients upon allergen challenge, with a greater amount of pDC recruited [28]. The identification of a human lung DC subset that can specifically direct inflammation to Th2 suppression will provide an effective approach to the treatment of asthma. Additional studies are warranted to examine the functional role of each DC subtype in allergic airway inflammation and asthma.

T-regulatory Cells in Allergic Airway Inflammation

T-regulatory cells (Tregs) are a heterogeneous group of cells that play a central role in maintaining the homeostasis of pulmonary immunity by establishing immune tolerance to nonharmful antigens or suppressing effector T-cell immunity. Naturally occurring $CD4^{+}CD25^{+}$ Tregs (nTregs) constitutively express CD25, a transmembrane protein and

an α-chain of the receptor for IL-2, and suppress autoimmune T-cell responses and maintain peripheral tolerance. They also constitutively express transcription factor forkhead box P3 (FoxP3), which prevents deviation of Tregs into effector T cells. The nTregs are generated in the thymus by positive selection in a process mediated by class II MHC-positive thymic cortical epithelium or DCs [29]. This development requires a higher-affinity TCR and IL-2 signal [29]. IL-2 presumably activates downstream effector STAT5 to regulate FoxP3 expression [30]. Peripheral differentiation of Tregs, namely inducible Tregs (iTregs), that secrete IL-10 requires a combination of strong TCR signal, high levels of TGF-β [31], and/or IL-10 (Fig. 1). In TGF-β-mediated induction of iTregs, cytotoxic T-lymphocyte-associated antigen-4, a competitive receptor of CD28 for the costimulatory molecules CD80 and CD86, is required [32]. The activity of Tregs is associated with the development of asthma. Adoptive transfer of antigen-specific $CD4^+CD25^+$ T-regs attenuates acute allergic airway inflammation, AHR, and airway remodeling in an IL-10-dependent manner [33]. We recently reported that both nTregs and iTregs reverse established cockroach antigen-induced allergic asthma, but the effect of iTregs depends on higher levels of TGF-β, IL-10, and IFN-γ, and elevated levels of programmed death-1 than are seen in nTregs to differentiate into IL-10—producing iTregs in the lung to exert their suppressive activity [34•]. Although TGF-β plays a detrimental role in promoting airway remodeling, the cooperation between IL-10 and TGF-β seems to be important in iTreg-mediated immune suppression. These data suggest that one of the treatment options would be to enhance $CD4^+CD25^+$ Tregs in addition to targeting decreased Th2 populations.

Role of $CD8^+$ T Cells in Allergic Airway Inflammation

The investigations into the contribution of cytotoxic $CD8^+$ T cells to the development of allergic airway inflammation remain inconclusive. On one hand, a body of evidence has suggested that $CD8^+$ T cells, which play a key role in cellular immunity by secreting IFN-γ and cytolytic factors, have a suppressive effect on allergic airway inflammation. $CD8^+$ T cells inhibited the allergen sensitization in a rodent animal model [35]. The late allergic response and airway inflammation induced by adoptive transfers of $CD4^+$ T cells is abolished by the resident $CD8^+$ T cells. MHC class-restricted, allergen-specific $CD8^+$ T cells are generated in draining lymph nodes upon allergen challenge and rapidly infiltrate into the lung. These cells suppress the features of allergic airway inflammation by inducing IL-12 production [36]. The Th2-suppressive effect of antigen-specific $CD8^+$ T cells in an animal model immunized with OVA-CLDC (cationic liposome-DNA complexes) vaccine is dependent on IFN-γ production [37]. Two types of $CD8^+$ T cells, classified by TCR αβ and γδ, have functional distinction. $CD8^+$ T cells with γδ TCR are inhibitory in allergic asthma [38]. The mediator of this suppressive effect on late allergic airway responses and eosinophilia has been proven to be IFN-γ as well (Fig. 1) [38]. On the other hand, $CD8^+$ T cells seem to be actively involved in the induction of allergic airway inflammation, as demonstrated by the use of knockout mice deficient in $CD8^+$ T cells. These mice demonstrated decreased AHR and airway inflammation and lower IL-13 production in the BALF in response to allergen challenge compared with wild-type mice [39]. This finding suggests that $CD8^+$ T cells are required for full development of these responses and that this process is IL-13 dependent. A later study revealed that although $CD8^+$ T cells are not absolutely required at the initiation stage of allergic airway inflammation, unlike $CD4^+$ Th2 cells, their absence seems to contribute to a lesser degree of AHR, airway eosinophilia, inflammatory cytokine production in BALF, and goblet cell metaplasia in a long-term sensitization protocol, suggesting a more active role for $CD8^+$ T cells in the chronic phase of allergic airway inflammation as compared to their importance in acute allergic reaction [40]. A subset of $CD8^+$ T cells, named *Tc2 cells*, can produce Th2 cytokines such as IL-4, IL-5, and IL-13, which are increased in the BALF of allergic asthmatic patients (Fig. 1) [41]. This leads to a concept that different types of $CD8^+$ T cells function in such a way that favors a specific direction of immune response. In fact, two different antigen-experienced T-cell subsets have been described. They can be distinguished by their ability to home to lymphoid organs (central memory cells with a phenotype of high levels of CD62 ligand and CCR7) or nonlymphoid tissues and site of inflammation and acquire effector cell function more rapidly (effector cells with a phenotype of lower levels of CD62 ligand and CCR7) [42]. Effector memory $CD8^+$ T cells, but not central memory $CD8^+$ T cells, are essential to the development of AHR and airway allergic inflammation in adoptive transfer models [43]. This may be due to the preferential localization of the effector cells to the lungs. Additionally, the $CD8^+$-mediated AHR and airway inflammation are dependent on Th2 cells and IL-4 [44]. The concept of $CD8^+$ Tregs has been raised, and T-cell phenotypes such as in vitro-generated $CD8^+CD28^-FoxP3^+$ suppressor T cells [45], tonsillar $FoxP3^+CD8^+$ T cells [46], lymph node/spleen $CD45RC^{low}CD8^+FoxP3^+CTLA\text{-}4^+$ T cells [47], and $CD8^+CD25^+$ T cells [48], have been shown to have regulatory properties in different experimental settings. Whether they are present and involved in the regulation of allergic inflammation has yet been completely

elucidated. Thus, $CD8^+$ T cells exhibit functional and phenotypic plasticity.

Allergic Airway Inflammation and Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are enzymes that participate in extracellular matrix remodeling and degradation. Alteration in the regulation of MMPs is implicated in inflammatory processes. Their proteolytic cleavage of chemokines alters the chemokine gradient and inflammatory cell recruitment. Elevated levels of MMP-2 and MMP-9 have been observed upon allergen challenge, and they are considered crucial to the infiltration of inflammatory cells such eosinophils [49]. MMP-9 is associated with airway remodeling, including peribronchial fibrosis [50]. However, other studies have shown that MMP-9—deficent mice develop enhanced pulmonary inflammation and airway hyperactivity [51]. This is explained by its dominant role in controlling the resolution and egression of inflammatory cells in conjunction with MMP-2 [52]. MMP-2 and MMP-9 differentially regulate chemotaxis of airway inflammatory cells via proteolytic processing of chemoattractant in the airways and facilitate the clearance of these cells. One of the sources of MMP-9 is activated airway neutrophils [53]. In addition, MMP-12 has been shown to be involved in the accumulation and survival of the airway eosinophils and infiltration of neutrophils and macrophages, but not T cells, in a cockroach-sensitized murine model [54]. MMP-7 is also expressed in asthmatic lungs, and its deficiency results in attenuated allergic airway inflammation. MMP-7 has been shown to play a proinflammatory role by activating IL-25 and inhibiting retinoid-dependent development of Tregs [55]. Some attempts have been made to target MMPs in an asthmatic condition. The tissue inhibitor of metalloproteinase-1 and a synthetic MMP inhibitor, marimastat, could have a therapeutic effect in the treatment of asthma [56].

Asthma and Genes

Asthma is a polygenetic disorder. Susceptibility depends on differences in several genetic loci. Positional cloning has made it possible to identify a few susceptibility genes. The T-cell immunoglobulin domain, mucin-like domain (*TIM*) gene family [57], and a disintegrin and metalloproteinase domain 33 gene (*ADAM33*) [58] found on chromosome 20p13 are associated with asthma and AHR. The subsequent studies using anti-*TIM-1* in an allergic airway inflammation animal model yielded the expected effects [59]. *ADAM33* is important in the development, disease progression, and airway remodeling of asthma [60]. One study revealed the susceptibility gene *GPRA* (G-protein-coupled receptor for asthma susceptibility) for asthma found on chromosome 7p [61]. However, an epidemiologic study revealed that the *PTGDR* gene is not a significant risk factor for asthma among Puerto Ricans, Mexicans, or African Americans [62]. Dipeptidyl peptidase 10 (*DPP10*) and PHD finger protein 11 (*PHF 11*) have been linked to asthma and related phenotypes [63]. A recent genome-wide association study of asthma identified cyclic adenosine monophosphate—specific (phosphodiesterase E_3 dunce homologue, *Drosophila*) gene (*PDE4D*) as an asthma susceptibility gene, and phosphodiesterase E_4 inhibitors have been developed as medications for asthma [64]. In addition, genetic-epidemiologic studies have shown that the *ORMDL3* locus is a risk factor for asthma [65], and the *OPN3* on chromosome 1qter is an asthma susceptibility gene [66]. It should be noted that the importance of an asthma susceptibility gene should be considered within a specific ethnic context because of the genetic differences among various ethnic groups.

Role of the Coagulation System in Airway Inflammation

The interaction among inflammation-dependent tissue injury and thrombin formation, fibrin deposition, and impaired fibrinolysis has been shown in several pathologic conditions. Inflammatory cytokines such as tumor necrosis factor-α, eotaxin, and RANTES (regulated on activation, normal T-cell expressed and secreted) decrease the expression and activity of activated protein C, which plays a protective role in lung and airway remodeling [67]. Allergic airway inflammation disturbs the balance in blood coagulation and fibrinolysis and results in the accumulation of extravascular fibrin, plasma exudates, and inflammatory cells, leading to airway closure. Increased concentrations of tissue plasminogen activator antigen, plasmin-antiplasmin complex, and fibrinogen/fibrin degradation products have been observed in patients with untreated asthma. Hataji et al. [67] observed a significantly decreased ratio of activated protein C and thrombin and a decreased ratio of activated protein C and protein C, with increased concentrations of soluble thrombomodulin in the sputum of asthmatic patients compared with that of healthy volunteers. In another study, Wagers et al. [68] reported the deposition of fibrin along the luminal surface of the distal airway in a patient who died from *status asthmaticus*. This suggests increased activity of the fibrinolysis system in asthmatics. Aerosolized tissue plasminogen activator, a fibrinolytic agent, has been observed to diminish AHR in a murine model of allergic airway inflammation [68]. Furthermore, treatment with activated protein C significantly inhibited the development of lung fibrosis in bleomycin-induced lung

injury and the development of AHR and allergic airway inflammation in a murine model of asthma [69]. Overall, these studies suggest a role for disordered coagulation and fibrinolysis in the pathogenesis of asthma.

Novel Therapeutic Modalities

Currently, asthma treatment still largely relies on anti-inflammatory corticosteroids and bronchodilators such as β_2-adrenergic receptor agonists. In fact, many immune cells and mediators that contribute to the exacerbations and progress of allergy and asthma are potential modalities to treat the disease. The counterregulation relationship of Th1 and Th2 implies that manipulating the Th1/Th2 balance may be a potential approach to treating asthma, but the role of Th1 activation in allergic airway inflammation seems to be controversial. Adoptive transfer of Th1 cells causes an IFN-γ-mediated antieosinophilic effect [70]. The coexistence of adoptively transferred antigen-specific Th1 and Th2 cells reversed bronchial hyperresponsiveness and bronchoalveolar lavage eosinophilia in an IFN-γ—dependent fashion [71]. Furthermore, Th1 cytokine treatment in both human [72] and animal asthmatic murine models [73] has consistently shown a Th2-suppressive effect, including reduced AHR, airway eosinophilia, and IgE production. More recently, some known Th1-prone antigens, such as *Bacille Calmette-Guérin* [74] and cytosine-phosphorothiolated guanine oligodeoxynucleotides [75], have been studied as novel therapeutic strategies for the prevention and treatment of atopic conditions, with very promising therapeutic effects. The opposite findings [76, 77], however, weaken the validity of using Th1 cells and Th1 cytokines as an effective antiasthma treatment [78]. In fact, although no consensus has been reached regarding neutrophilia in Th1-induced airway inflammation [79], Th1 cells do induce hyperresponsiveness and lung fibrosis that are associated with IL-18 and antigen challenge [80, 81]. In a chronic allergic asthma model, IFN-γ and IFN-γ-producing $CD4^+$ cells in peripheral lymph nodes are maintained at high levels. Therefore, the controversial role of Th1 cytokine IFN-γ in allergic airway inflammation leads to caution in the application of Th1 to counteract Th2-dominant allergic airway inflammation [82].

Administration of certain Toll-like receptor ligands activates innate immunity and induces high levels of indoleamine 2,3-dioxygenase, the rate-limiting enzyme of tryptophan catabolism in various organs. Pulmonary indoleamine 2,3-dioxygenase activity in the lung cells in response to Toll-like receptor-9 activation has been shown to inhibit Th2-driven allergic airway inflammation and AHR [83]. These data suggest the pivotal role for the activation of innate immunity in inhibiting allergen-specific immune responses due to Th2 cytokines.

The role of calcium-activated potassium channel in the development and induction of asthma has drawn a great deal of attention due to its suitability for regulating membrane potential in cells with nonexcitable membranes—such as immune, epithelial, and endothelial cells—under inflammatory conditions. A growing body of evidence has linked the KCa3.1 activity to the migration, activation, and proliferation of the key cells in allergic inflammation, including T lymphocytes [84], mast cells [85], macrophages [86, 87, 88•], and smooth muscle cells [89]. Our data (unpublished) also suggest that KCa3.1 activity is associated with migration and antigen uptake of a lung-immunogenic DC subset. The application of TRAM-34, a low toxic KCa3.1—specific blocker with low toxicity, has been proven effective and safe in preventing the formation of atherosclerosis in a murine model [88•].

The novel immunomodulator Flt3-ligand (Flt3-L) suppresses Th2 responses in a murine model of allergic asthma. The therapeutic effect of Flt3-L is achieved by facilitating the generation of a regulatory $CD11c^{high}$ $CD11b^{low}$ lung DC subset, impairing migration of an immunogenic $CD11c^{low}CD11b^{high}$ DC subset to draining lymph node and antigen uptake in an immunogenic $CD11c^{low}CD11b^{high}$ DC subset [9••], [90–92], and increasing the density of $CD4^+CD25^+FoxP3^+ICOS^+$ Tregs in the lungs of asthmatic mice [93]. Thus, Flt3-L may prove to be a novel adjuvant therapy in bronchial asthma. Likewise, compounds that can balance the function of DCs and increase the activity of FoxP3-expressing Tregs have been under development. Local administration of the sphingosine 1-phosphate receptor agonist FTY720 to lung attenuates experimental asthma by inhibiting lung DC function [94], but a recent study indicated that FTY720 potentially inhibits Tregs' proliferation as well [95]. An early study showed that prostaglandin D_2 impaired the activation, differentiation, and migration of human DCs [96]. A recent study revealed that the activation of the D prostanoid 1 receptor by a selective agonist effectively suppressed asthma by regulating DC function and the generation of Tregs [97]. Obviously, more careful studies would confirm/refute their potential therapeutic effects in allergic airway inflammation and asthma.

Conclusions

Asthma is a multifactorial disease characterized by chronic airway inflammation and increased bronchoconstrictory response to nonspecific stimuli. Although there is a propensity for Th2 cytokines in asthmatic lungs, evidence

suggests a predominant role for local immune events in allergic airway inflammation. Allergen-specific DCs and Tregs seem to play a pivotal role in balancing tolerance versus immunologic response to allergens. Therapy with immunomodulators that do not elicit autoimmune response but enhance tolerance to allergens and increase Tregs would be most effective in the treatment of allergy and asthma.

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- •• Of major importance

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