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Mechanisms in allergic airway inflammation – lessons from studies in the mouse

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Asthma is a chronic inflammatory disease of the airways, involving recurrent episodes of airway obstruction and wheezing. A common pathological feature in asthma is the presence of a characteristic allergic airway inflammatory response involving extensive leukocyte infiltration, mucus overproduction and airway hyper-reactivity. The pathogenesis of allergic airway inflammation is complex, involving multiple cell types such as T helper 2 cells, regulatory T cells, eosinophils, dendritic cells, mast cells, and parenchymal cells of the lung. The cellular response in allergic airway inflammation is controlled by a broad range of bioactive mediators, including IgE, cytokines and chemokines. The asthmatic allergic inflammatory response has been a particular focus of efforts to develop novel therapeutic agents. Animal models are widely used to investigate inflammatory mechanisms. Although these models are not perfect replicas of clinical asthma, such studies have led to the development of numerous novel therapeutic agents, of which some have already been successful in clinical trials.

Asthma is a chronic inflammatory disease of the airways affecting approximately 300 million individuals worldwide (Ref. 1). The prevalence of asthma increased dramatically in many Western countries during the last 30 years of the 20th century and is now greater than 10% (Ref. 2). In several Western countries, the rates of asthma have reached a plateau since the 1990s, especially in adults (Ref. 3). Nevertheless, the high incidence of asthma represents a huge economic burden. For example, the cost to the US economy attributable to asthma was estimated to be US$12.7 billion in 1998 (Ref. 4). Furthermore, high levels of nonatopic asthma have been recognised in the developing world (Ref. 5).

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Asthma involves recurrent episodes of airway obstruction and wheezing, ranging in severity from mild to life-threatening. The majority of asthmatics have a characteristic allergic inflammatory response in the lungs involving excessive activation of T helper 2 (Th2) cells, eosinophil infiltration, mucus overproduction, and airway hyper-reactivity. In many cases, this results from an allergic response to environmental allergens (Ref. 6). It is important to note that asthma is highly heterogeneous, and that the asthmatic inflammatory response does not always correspond closely to classical allergy. For example, a significant number of asthmatics have an inflammatory pathology dominated largely by neutrophils rather than eosinophils (Ref. 7). The heterogeneity of asthma is beyond the scope of this review, and we focus here principally on the cellular and molecular mechanisms underlying allergic airway inflammation (AAI).

Animal studies have been valuable for elucidating the cellular and molecular pathways required for AAI. Murine models have been particularly useful, because of the many tools available to dissect mechanisms of allergic inflammation. Neutralising antibodies, transgenic mice (usually overexpressing selective genes) and knockout mice (lacking selective genes) are particularly powerful in assessing the role of individual molecules and cells (Ref. 8). The popularity of such models needs to be considered against their limitations (Ref. 9). There are many structural and functional differences between mice and humans, and mice do not spontaneously develop asthma. Experimental AAI is usually induced artificially by parenteral administration of allergen in adjuvant. Furthermore, in a standard murine AAI model, degranulated eosinophils are detected only in the airway lumen and not in the lung tissue (Ref. 10).

The vast majority of animal studies assess acute responses to inhalation of high concentrations of antigen, which generate vigorous cellular infiltration but are not good models of airway remodelling, a common feature of established asthma. A chronic model has been developed that has more histological similarities to clinical asthma (Ref. 11). In another chronic model, mice were followed for several weeks after cessation of challenge. AAI resolved, but airway hyper-responsiveness (AHR) and remodelling did not resolve during the period of observation (Ref. 12). There are, however, relatively few studies on chronic allergen exposure. Furthermore, the standard mouse models do not reliably demonstrate the early- and late-phase responses that are characteristic of clinical asthma (Ref. 13). Finally, results in mouse models may differ markedly between strains, making it difficult to extrapolate findings to clinical asthma. Despite these limitations, mouse models are widely used to identify potential targets and to assess new therapeutic agents (Refs 8, 14). This review draws heavily on animal models of AAI. Clinical trials of novel therapeutic agents are also included, but we do not attempt a comprehensive coverage of descriptive clinical studies.

Differentiation of effector T helper cells

$CD4^+$ Th cells are necessary for the pathogenesis of AAI. Depletion of murine $CD4^+$ T cells prevents antigen-induced pulmonary eosinophilia and AHR (Ref. 15). The Th2 subset, which controls the allergic response through the production of cytokines such as interleukin (IL)-4, IL-5, IL-9 and IL-13, is particularly prominent in allergic asthma (Refs 16, 17). The key role of Th2 cells is illustrated in Figure 1. Differentiation of naive $CD4^+$ T cells is a tightly regulated process. Experiments in mice have demonstrated that the cytokine microenvironment has a major role in regulating T cell differentiation, but other factors such as antigen concentration, and expression of costimulatory molecules and Notch ligands, also contribute (Refs 18, 19).

IL-4 signalling through STAT6 (signal transducer and activator of transcription 6) was originally thought to be necessary for Th2 cell commitment (Refs 20, 21). It is now apparent that Th2 cell differentiation can occur in the absence of both IL-4 and STAT6. Nevertheless, STAT6 is essential for eosinophilic inflammation and Th2 cell tracking to the lung in murine AAI (Refs 22, 23), and in clinical asthma, phosphorylated STAT6 is increased in peripheral blood memory $CD4^+$ T cells, and it decreases after therapy with oral corticosteroids (Ref. 24). The transcription factor GATA-3 is the master regulator of Th2 cell development (Ref. 25). GATA-3 regulates expression of other well-described Th2 differentiation transcription factors – c-MAF, NF-ATc (nuclear factor of

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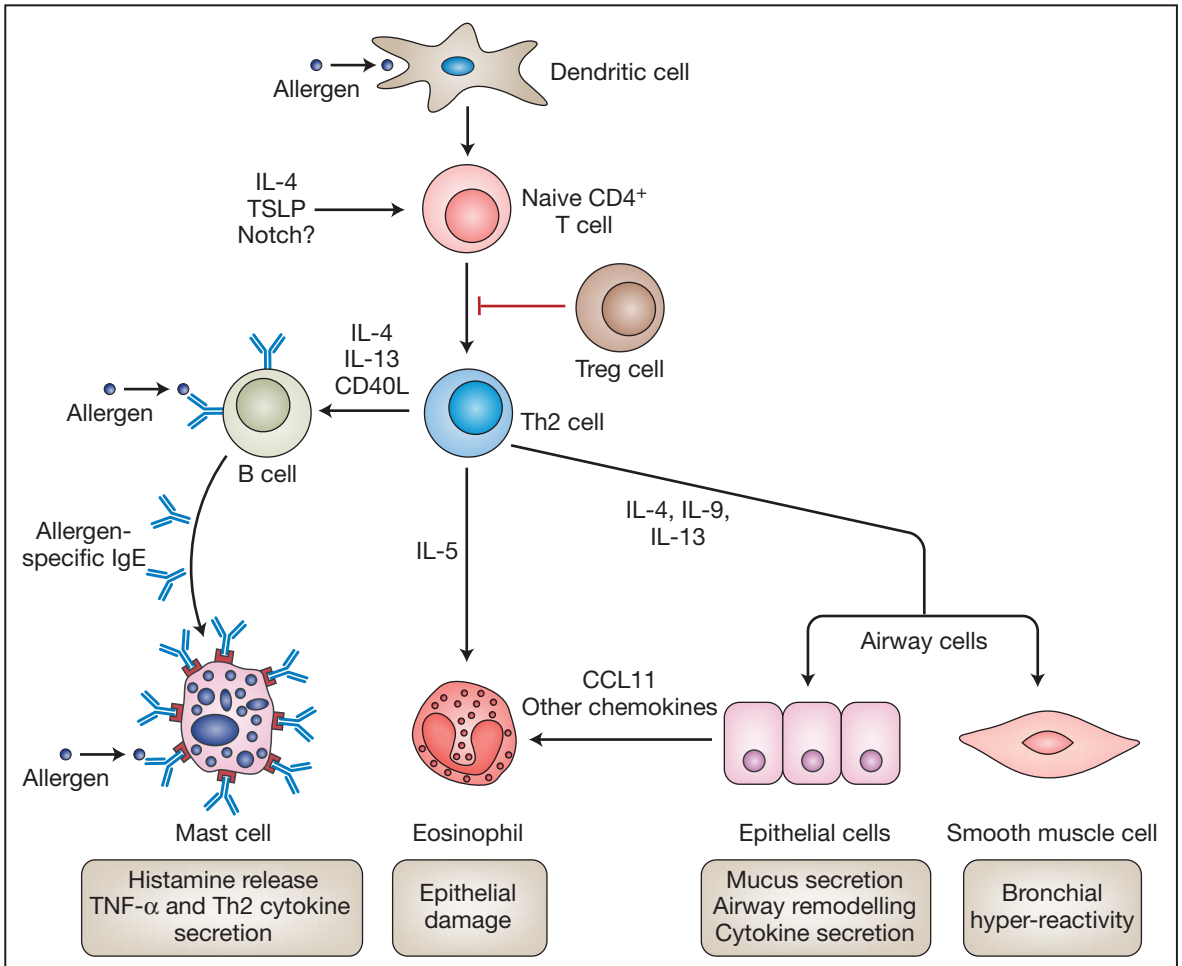

Figure 1. Cytokine regulation of allergic asthma. Pulmonary dendritic cells process and present inhaled antigens to naive $CD4^+$ T cells. Generation of Th2 cells is enhanced by the presence of the cytokines IL-4 and TSLP, and is influenced by Notch ligands. Secretion of IL-4 by naive T cells contributes to their differentiation into Th2 cells. Th2 cells secrete IL-4 and IL-13, and express CD40L, to stimulate IgE production by B cells. IgE binds to Fc receptors on the surface of mast cells. When mast cells are activated by antigen-dependent crosslinking of IgE receptors, they degranulate, releasing histamine and TNF-α, and they secrete cytokines including IL-4 and IL-13. Eosinophil survival is supported by IL-5, and CCL11 (eotaxin-1) and other cytokines attract eosinophils to the airways. Eosinophils are toxic to epithelial cells. IL-4, -9 and -13 promote airway hyper-reactivity, mucus secretion and cytokine secretion by epithelial cells. Regulatory T cells (Treg) suppress the activation and differentiation of naive $CD4^+$ T cells. Abbreviations: IL, interleukin; TSLP, thymic stromal lymphopoietin.

activated T cells c) and STAT6 (Refs 26, 27, 28) – and controls Th2 differentiation through epigenetic transactivation of promoter regions of the genes for IL-4, IL-5 and IL-13 (Refs 25, 29). The signals that initiate GATA-3 expression during antigen priming of a naive $CD4^+$ T cell remain unclear. One possible mechanism may be through the Notch signal transduction pathway. This pathway regulates cell differentiation in many different tissues. Cell-surface Notch receptors can be engaged by ligands of the Delta-like or Jagged families. Expression of Delta-like or Jagged ligands on dendritic cells was elicited by Th1- and

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Th2-inducing stimuli, respectively (Ref. 19). Engagement of Notch on $CD4^+$ T cells by Jagged on dendritic cells favoured Th2 differentiation and IL-4 production. Under these conditions, Notch induced GATA-3 and stimulated IL-4 transcription via the transcription factor RBP-Jκ (Jκ recombination signal sequence binding protein) (Refs 19, 30). In the absence of GATA-3, Notch signalling promoted naive $CD4^+$ T cells to differentiate to Th1 cells (Ref. 31).

For a naive T cell, an alternative pathway to Th2 commitment is polarisation into the Th1 lineage. Signalling through interferon (IFN)-γ and the T-bet transcription factor (encoded by *TBX21*) has been identified as the major pathway that determines Th1 differentiation, while the IL-12–STAT4 pathway also plays an important but lesser role (Refs 32, 33, 34). T-bet is essential for Th1 cell differentiation and commits naive T cells to this lineage by repressing GATA-3 expression (Ref. 35). The lungs of naive T-bet-knockout ($Tbx21^{-/-}$) mice have a striking phenotype indicative of a Th2-dominated environment, including prominent perivascular and peribronchial eosinophilia, extensive airway remodelling and increased AHR (Ref. 36). The lung phenotype of these mice emphasises the critical role of Th2 cells in AAI. In patients with clinical asthma, reduced peripheral blood mononuclear cell T-bet mRNA expression has been reported (Ref. 37).

While the Th1–Th2 paradigm is over two decades old, a third, distinct Th cell subset has recently been recognised. The Th17 subset is defined on the basis of secretion of the cytokine IL-17, now known as IL-17A, which has been particularly associated with neutrophilic inflammation. Th17 cells also produce IL-17F, which has a number of similar effects to IL-17A (Ref. 38). The transcription factors RORγt (retinoic-acid-related orphan receptor γt) and STAT3 are essential for the development of Th17 cells, and RORγt appears to be the Th17 cell counterpart of GATA-3 in Th2 cells and T-bet in Th1 cells (Refs 38, 39). Human T cells require exposure to IL-1β and IL-6 to induce RORγt (Ref. 40), whereas in mice the necessary factors are transforming growth factor β (TGF-β) and IL-1β (Ref. 41) or TGF-β and IL-21 (Ref. 42). Once differentiation along the Th17 pathway has been induced, the cells expand in the presence of IL-23 (Ref. 43). The role of RORγt in AAI has not yet been reported. Studies on the role of IL-17A in asthma are reviewed below.

Regulatory T cells

Regulatory T cells (Treg) are another important subset of $CD4^+$ T cells. While Treg have been most extensively studied in autoimmune diseases, there is now abundant evidence that Treg are an integral component of all immune responses, including allergic reactions (Ref. 44). The best-described Treg develop in the thymus and are termed naturally occurring or nTreg. These arise from a distinct developmental pathway, which depends on the production of thymic stromal lymphopoietin (TSLP) by Hassall's corpuscles in the thymic medulla. TSLP, a cytokine related to IL-7, stimulates dendritic cells, which are necessary for nTreg development (Ref. 45). nTreg are best characterised by expression of the transcription factor FOXP3 (forkhead box P3). Other populations of Treg, collectively known as inducible Treg, develop in the periphery from antigen-exposed effector T cells and may also express FOXP3 (Ref. 44). The most widely used surface marker to identify Treg is the alpha chain of the IL-2 receptor (CD25), although activated effector T cells also express CD25 (Ref. 46). In humans, Treg can be distinguished from activated effector T cells because Treg express much lower levels of the surface marker CD127. $CD127^{lo}CD25^+$ Treg make up 6% of blood $CD4^+$ T cells in healthy individuals (Ref. 47). nTreg principally mediate immunosuppression via cell–cell contact, whereas inducible Treg may mediate inhibitory effects by secretion of the immunosuppressive cytokines IL-10 and TGF-β (Ref. 44).

A role for Treg has been demonstrated in studies on mouse models of AAI. In one approach, antigen-specific $CD4^+CD25^+$ Treg cells were transferred into antigen-sensitised animals prior to challenge. The Treg reduced the resulting AHR, lung eosinophil infiltration, and Th2 cytokine production (Ref. 48). These effects depended on IL-10 production in the recipient, but did not require IL-10 production by the Treg themselves. In an alternative approach, depletion of Treg with an anti-CD25 antibody prior to antigen sensitisation increased AHR, eosinophil infiltration and Th2 cytokine production, and elevated the capacity of pulmonary dendritic cells to elicit a Th2 response (Ref. 49). In another

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study, when mice were treated with cyclophosphamide prior to sensitisation, the resulting pulmonary eosinophil infiltration and Th2 response were greatly increased, and this was associated with a reduction of FOXP3 expression in the lungs and lymphoid organs, suggesting that cyclophosphamide depletes Treg (Ref. 50). In a model of tolerance induced by respiratory exposure to allergen, pulmonary dendritic cell production of IL-10, and the resulting production of IL-10 by Treg, was required for the induction of mucosal tolerance (Ref. 51). In a rat model of chronic aeroallergen exposure, Treg appeared in the respiratory mucosa and regional lymph nodes within 24 h of initial antigen exposure, and prevented further AHR (Ref. 52). Taken together, these animal studies indicate that Treg inhibit the extent of allergic inflammation.

There is emerging evidence that Treg can control Th2 responses in humans. $CD4^+CD25^+$ blood T cells from nonatopic donors inhibited antigen-stimulated IL-5 production by $CD4^+CD25^-$ T cells, whereas inhibition by $CD4^+CD25^+$ T cells from atopic donors was much less effective (Ref. 53). In a study on cytokine production by individual blood T cells, the dominant allergen-specific cells were IL-10-secreting in healthy individuals, resembling a type of inducible Treg known as T regulatory 1 (Tr1) cells. By contrast, in atopic individuals, the most abundant allergen-specific cells were Th2-like IL-4 secretors (Ref. 54). Both these papers propose that atopy may be associated with an imbalance between Th2 cells and Treg.

The effects of Treg could account for some of the observations associated with the 'hygiene hypothesis'. This hypothesis attempts to explain the recent increased incidence of asthma in developed countries on the basis of reduced exposure to infectious agents, especially during early life. Early studies suggested that skewing of the Th response towards Th2 and away from Th1, because of reduced exposure to Th1-inducing pathogens, was a major contributor to increased asthma incidence. However, several observations argue against this. First, there is increasing evidence that in asthma in humans, and AAI in animals, Th1 cytokines contribute to pathogenesis (see section 'Th1 cytokines' below). Second, the incidence of several Th1-cytokine-driven inflammatory diseases such as type 1 diabetes also increased in the late 20th century (Ref. 55). Third, high parasite burdens, which are associated with strong Th2 inflammation, can protect against allergic disease (Ref. 56).

An alternative proposal relates the increasing incidence of asthma in developed countries to diminished Treg function (Ref. 57). Infection with helminth parasites induces vigorous Th2 responses and Treg cells. In mice, infection with the gastrointestinal nematode *Heligmosomoides polygyrus* provided significant protection against AAI (Ref. 58). Remarkably, protection could be conferred following transfer of helminth-induced Tregs into uninfected allergen-sensitised mice. IL-10 is required for helminth-induced protection against AAI (Ref. 59). It is therefore possible that the low incidence of parasite infection in developed countries leads to lower generation of Treg and enhanced Th2 responses.

Dendritic cells

Antigen uptake and presentation to naive T cells is principally mediated by dendritic cells. Generation of effector T cells by respiratory dendritic cells is skewed towards a default Th2 programme (Ref. 60), generating robust Th2 effector function to provoke airway and lung tissue eosinophilia (Ref. 61). In addition to activation of the T-cell receptor, costimulatory signals are required for activation of naive T cells. The best-described costimulatory pathway involves the B7 molecules CD80 and CD86 on dendritic cells, which activate CD28 on T cells. In a mouse model, CD80 and CD86 were required for efficient T-cell priming and Th2 cytokine secretion during sensitisation to antigen, but not during antigen challenge (Ref. 62). However the effects of costimulation are complex, because antibody crosslinking of B7 on dendritic cells, which activates them, has been reported to inhibit airway inflammation in a mouse model (Ref. 63). CTLA4-Ig (abatacept), which contains a natural ligand of CD80 and CD86 that binds to these markers and blocks their costimulatory function, was trialled in active rheumatoid arthritis. CTLA4-Ig caused marked clinical and functional improvement in patients in whom at least three months of therapy with tumour necrosis factor (TNF) blockers was unsuccessful (Ref. 64). These findings raise the possibility that CTLA4-Ig may be beneficial in asthma, although it must

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be recognised that rheumatoid arthritis is not a Th2 disorder.

Priming of naive $CD4^+$ T cells by dendritic cells towards a Th1 or Th2 phenotype is also affected by the presence of the cytokine TSLP (Ref. 65), which not only acts directly on naive $CD4^+$ T cells to enhance proliferation and survival (Ref. 66) but also can upregulate costimulatory molecule expression on antigen-presenting dendritic cells. Furthermore, $CD4^+$ T cells primed from TSLP-treated dendritic cells produced significantly less IFN-γ (Ref. 67). The importance of TSLP for the development of allergic asthma was demonstrated by the attenuated inflammatory response of TLSP-receptor-knockout mice in an asthma model, and also by the protection of wild-type mice against the asthma phenotype when TSLP was neutralised in the lungs (Ref. 67). In patients with asthma, the number of airway cells expressing TSLP was increased, and correlated with airway obstruction. TSLP was expressed by epithelial cells, endothelial cells, neutrophils, mast cells and macrophages (Ref. 68). Epithelial cells are a major source of TSLP, highlighting the important overlapping functions between innate and adaptive immunity for Th1- or Th2-directed responses (Ref. 69).

The role of dendritic cell expression of Notch ligands in Th1 and Th2 differentiation is reviewed above in 'Differentiation of effector T cells'.

Eosinophils

Airway eosinophilia is a key feature of AAI. Eosinophils produce leukotriene (LT) C4, major basic protein and a broad range of cytokines and proallergic mediators (Ref. 70). However, there are conflicting results on the association between eosinophils and AHR. In some studies, using IL-5-knockout mice or neutralising anti-IL-5 antibody, in which eosinophils were depleted, AHR was abolished (Refs 71, 72). However, other reports failed to demonstrate an association between eosinophilia and AHR. In a study on mice treated with anti-IL-5 antibody, eosinophils were depleted but AHR was not affected (Ref. 73), and other mouse models of AAI have been reported in which eosinophils were not required for AHR (Refs 74, 75).

Findings in recently developed eosinophil-deficient mice have also been controversial. In one strategy for generating eosinophil-deficient mice, knockout of a high-affinity GATA site in the GATA-1 promoter effectively deleted eosinophils but not other leukocyte lineages. Assessment of these 'ΔdblGATA' mice in AAI revealed that loss of eosinophils did not affect mucus hypersecretion or AHR, although subepithelial collagen deposition was reduced after prolonged allergen challenge (Ref. 76). A second eosinophil-deficient mouse strain was developed by ectopic expression of diphtheria toxin A chain under the eosinophil peroxidase promoter. When examined in a model of allergic asthma, these 'PHIL' mice had a modest reduction in mucus secretion and complete reversal of AHR (Ref. 77). By contrast to evidence presented with the ΔdblGATA mice, these findings suggest a direct role for eosinophils in causing key asthma pathologies. One explanation for the discrepant results could lie in the differing genetic backgrounds of the two strains. The ΔdblGATA mice were bred on the Th2-susceptible BALB/c background while the PHIL mice originated from the Th2-resistant C57BL/6 background. These discrepant results highlight limitations in the capacity of mouse models to predict mechanisms in human asthma. The role of eosinophils in AAI remains controversial. Furthermore, human studies have failed to demonstrate a causal relationship between eosinophil infiltration and asthma (see section 'IL-5' below).

Mast cells

Along with eosinophils, another enigmatic cell type in asthma is the mast cell. These cells are packed with a host of preformed inflammatory molecules including histamine, TNF-α, and tryptases and chymases, which are serine proteases. Granule contents are released in response to numerous stimuli, of which the most relevant to AAI is crosslinking of the high-affinity IgE receptor (FcεR1), and also perhaps Toll-like receptor signalling (Ref. 78). In addition to preformed mediators, mast cells also secrete de novo synthesised cytokines, chemokines and inflammatory lipids after activation (Ref. 79, 80). In clinical asthma, mast cells produce the key Th2 cytokines IL-4, IL-5 and IL-13 (Refs 81, 82), although the relative contribution of mast cells versus Th2 cells to the production of these cytokines is controversial.

Investigations on the requirement for mast cells in murine AAI have given conflicting results (Refs 83, 84, 85). In clinical studies, the efficacy

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of an anti-IgE neutralising antibody has indirectly implicated mast cells in the pathogenesis of human allergic asthma. The humanised antibody omalizumab binds to the CH3 domain of IgE, preventing IgE from binding to both FcεRI (high-affinity) and FcεRII (low-affinity) IgE receptors (Ref. 86). Omalizumab inhibited both the early and late asthma responses to allergen, and reduced the levels of circulating IgE (Ref. 87). It reduced sputum and tissue eosinophilia and IgE^+ and $Fc\varepsilon RI^+$ cells in the bronchial mucosa (Ref. 88). Although omalizumab is clinically very effective in the treatment of asthma, its high cost has limited its usefulness to the most severe cases (Ref. 89). The findings suggest that mast cells are critical in the pathogenesis of clinical asthma, although the beneficial effects of omalizumab may involve other $Fc\varepsilon R^+$ cells.

Airway epithelial cells

The more sophisticated functions of airway epithelium that regulate lung inflammation are often overshadowed by its more mundane, yet important, function as a physical barrier to the external environment, and its role as a mucus secretory unit. Airway epithelial cells are responsive to many mediators involved in asthma, and activated airway epithelial cells express many chemokines, cytokines and other mediators known to promote AHR and airway inflammation and remodelling (Refs 90, 91). For example, airway epithelial cells release the neurotrophins nerve growth factor and brain-derived neurotrophic factor in response to inflammatory cytokines including TNF-α, IL-1β and IL-4 (Ref. 92). Nerve growth factor augments airway inflammation in a mouse model (Ref. 93). The extensive array of pro-inflammatory mediators produced by airway epithelial cells clearly demonstrates their role in lung inflammation and remodelling, but whether stimulation of these cells can independently induce aberrant AHR is unclear.

The airway epithelium is constantly exposed to inhaled antigens and environmental pollens that may trigger an asthmatic episode. Some of these external stimuli can directly modulate cellular function, thereby contributing to the initiation and maintenance of airway inflammation. For example, the Der p1 antigen of house dust mite activates protease-activated receptors on airway epithelial cells to induce IL-6, IL-8 and granulocyte–macrophage colony-stimulating factor (GM-CSF) expression (Refs 94, 95, 96). Interestingly, asthmatic airway epithelial cells produced more CCL20 [chemokine (C-C motif) ligand 20; also known as MIP-3α] after exposure to Der p1 than did control airway epithelial cells, indicating an intrinsic hypersensitivity of asthmatic epithelium to house dust mite allergens (Ref. 97). Pollen extracts have intrinsic NADPH oxidase activity that alters the redox status in airway epithelial cells, resulting in generation of more reactive oxygen species, which ultimately augments the development of AAI in mice (Ref. 98). Furthermore, protease activity in pollens such as ryegrass and Kentucky blue grass cause airway epithelial cell detachment in vitro, suggesting such proteases may disrupt airway epithelial integrity in vivo (Ref. 99).

There are few reports that specifically address the mechanisms of airway epithelial cell function in vivo in AAI. These studies have utilised the Clara cell 10 kDa secretory protein (CC10) promoter to specifically target gene expression in airway epithelial cells. Targeting of NF-κB signalling in the airway epithelium conclusively demonstrated a prominent NF-κB-dependent role for this cell type in the pathogenesis of AAI (Ref. 100). Similarly, tissue-specific gene targeting identified a requirement for STAT6-mediated responses in airway epithelial cells for the development of IL-13-driven AHR and mucus production (Ref. 101). Surfactant protein-A and -D are produced by alveolar epithelial cells, and administration of these molecules in mice led to reduced inflammation in an AAI model (Ref. 102). IL-4 and IL-13 induced high levels of expression of the fatty-acid-binding protein aP2 in airway epithelial cells. In a model of AAI, aP2-knockout mice had markedly reduced airway eosinophils, and bone marrow chimaera studies implicated nonhaematopoietic cells, most likely airway epithelial cells, in aP2 expression (Ref. 103). These findings suggest an intriguing link between asthma and fatty acid metabolism. Collectively, these studies demonstrate that airway epithelial cell function is vital in the pathogenesis of AAI.

Cytokines and chemokines

Cytokine regulation of AAI is complex, with a plethora of factors contributing to pathogenesis

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(Refs 104, 105, 106). Here we review the role of several key cytokines in AAI.

IL-4

IL-4 is an important cytokine for $CD4^+$ Th2 cell differentiation (Refs 21, 107) and IgE class switching (Ref. 108). IL-4 can bind to two surface receptor complexes: one formed by the IL-4Rα chain and the common γ cytokine receptor chain (γc), and the other formed by the IL-4Rα and the IL-13Rα chain. IL-13 also binds to the latter complex. Ligation of either receptor complex triggers signalling of STAT6 and other pathways (Ref. 109). The importance of IL-4 for Th2 cell priming during AAI was demonstrated by the reversal of allergen-induced AHR in mice treated with anti-IL-4 antibodies during both sensitisation and challenge stages, while treatment during antigen challenge alone did not confer protection (Ref. 73). In an experimental system involving transfer of OVA-specific $IL4^{-/-}$ Th2 cells into sensitised mice, IL-4 regulated airway eosinophilia but not mucus hypersecretion (Ref. 110). Mice deficient for IL-4 displayed attenuated airway eosinophilia, although different effects on AHR were reported in different models (Refs 111, 112), possibly reflecting the critical role on genetic background in the development of AHR in mouse models. In clinical studies, a soluble IL-4 receptor was administered weekly by nebuliser to asthma patients who discontinued inhaled steroids at the commencement of the study. The soluble IL-4 receptor demonstrated significant benefit in patient-measured FEV_1 (forced expiratory volume in 1 s) (Ref. 113), but these studies have not been followed up by publications on larger trials.

IL-5

The prominent airway and lung tissue eosinophilia in allergic asthma has led to a focus on the mediators that govern the production, survival and activation of eosinophils. IL-5 fulfils all these functions and is elevated in bronchoalveolar lavage fluid from human asthmatics and allergic mice (Refs 70, 114). IL-5 acts on bone marrow progenitors to accelerate the production of eosinophils (Ref. 115). $IL\text{-}5^{-/-}$ mice have a marked reduction in the number of eosinophils in the airway, lung tissue and peripheral blood in AAI (Ref. 72), although the requirement for eosinophils in murine AHR is controversial (see section 'Eosinophils' above). The effects of clinical studies with neutralising anti-IL-5 antibodies were disappointing. Treatment markedly reduced the levels of blood and sputum eosinophils in asthmatic patients, but did not affect AHR. These results argue against a role for eosinophils in the pathogenesis of asthma (Ref. 116). Similar results have been found in other trials with anti-IL-5 antibodies (Refs 117, 118). Furthermore, although anti-IL-5 treatment resulted in near-complete elimination of eosinophils from the blood and sputum, it reduced airway eosinophils only by 55%, suggesting that other factors may have maintained eosinophil viability in the airways (Ref. 119). These results have been discouraging for therapeutic approaches designed to target a single cytokine in allergic asthma.

IL-9

IL-9 has multiple actions similar to those of other Th2 cytokines, consistent with an effector role in AAI (Ref. 120). Transgenic mice with elevated pulmonary expression of IL-9 exhibit increases in inflammatory cell influx, mucus production and mast cell numbers (Ref. 121). IL-9 acts via IL-13 to induce mucus production and eosinophil chemoattraction by the pulmonary epithelium (Ref. 122). In two separate studies with mouse models of allergen-induced asthma, administration of neutralising anti-IL-9 antibodies was reported to reduce eosinophilia, AHR, airway damage and IgE (Refs 123, 124). However, different findings were obtained in IL-9-knockout mice, in which AHR, eosinophilia and goblet cell hyperplasia were not impaired in a model of allergic asthma (Ref. 125). Although the reasons for the differences are not clear, the results in the knockout mice have discouraged attempts to assess the effects of specific blockade of IL-9 in clinical asthma.

IL-13

IL-13 binds to the IL-4Rα–IL-13Rα1 receptor complex, as does IL-4, and shares many effects with IL-4 (Refs 126, 127). As mentioned above, IL-4 also signals through the receptor formed by the IL-4Rα chain and γc, and there is an additional IL-13 receptor chain, the IL-13Rα2 chain, which can act as a decoy receptor, inhibiting the effects of IL-13 (Ref. 128).

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Administration of recombinant IL-13 to the airways of naive mice strongly induces mucus secretion in airway epithelial cells and is sufficient to induce both airway eosinophilia and IgE production. Neutralisation of IL-13 with a soluble fusion protein prevents AHR in an AAI model in mice (Refs 127, 129). The crucial action of IL-13 acting directly at the level of the airway epithelium was demonstrated by a compelling study (Ref. 101), where overexpression of IL-13 restricted to the airway epithelium was sufficient to induce AHR and mucus production. The IL-13Rα2 chain has an important role in regulating AAI. In a model of AAI, mice lacking this receptor chain exhibited enhanced AHR, mucus production and fibrosis (Ref. 130).

The discovery that IL-4 and IL-13 share receptors has led to the development of a receptor antagonist molecule, pitrakinra, that inhibits both cytokines. It is an IL-4 variant that competitively inhibits receptor complexes containing the IL-4Rα chain, thereby interfering with the actions of both IL-4 and IL-13. In a recent report on patients with allergic asthma, administration of pitrakinra, either subcutaneously or by inhalation, reduced the late-phase response to allergen (Ref. 131). This report provides good evidence for a role for Th2 cytokines in clinical allergic asthma, and suggests that simultaneous inhibition of more than one Th2 cytokine may be necessary for beneficial effects.

Th1 cytokines

Type 1 cytokines such as IFN-γ and IL-12 inhibit Th2-cell differentiation and Th2 cytokine effector function. For this reason, Th1 cytokines were originally regarded as potentially protective against asthma, which was considered a purely Th2 response (Ref. 18). Interestingly, an attempt to inhibit the Th2 response in asthmatics through recombinant IL-12 therapy reduced airway eosinophil numbers but not AHR (Ref. 132), which indicates a more complicated role for Th1 cytokines in asthma than is suggested by the earlier Th1–Th2 imbalance paradigm. In fact, a number of studies have reported enhanced IFN-γ levels in asthmatic patients, suggesting that IFN-γ and Th1 cells may in fact be pathogenic in asthma (Refs 133, 134).

In mouse asthma models, while some studies showed protective effects of Th1 cells (Refs 36, 135), other experiments on transfer of Th1 cells into allergic mice failed to show Th1 suppression of Th2 cell function in vivo (Ref. 136). Instead of being protective, Th1 cells could potentially exacerbate inflammation (Ref. 137). Neutralising anti-IFN-γ antibodies in mouse models of asthma resulted in reduced AHR (Ref. 138, 139). These studies, taken together with the clinical studies described in the previous paragraph, suggest that Th1 cells and IFN-γ contribute to the pathogenesis of AAI and asthma.

IL-17A

In clinical asthma, IL-17A is overexpressed in the airways and is associated with neutrophil influx (Ref. 140). IL-17A induces the production by human airway smooth muscle cells of the neutrophil chemoattractant CXCL8 (IL-8) (Ref. 141) and the eosinophil chemoattractant CCL11 (eotaxin-1) (Ref. 142). In a mouse model of AAI, antibodies to IL-17A inhibited neutrophil influx but enhanced eosinophil influx (Ref. 143). In another mouse study, IL-17A was required during the sensitisation phase for the development of allergic responses, but it attenuated the allergic response during the effector phase (Ref. 144). These findings suggest that IL-17A is more likely to be a therapeutic target in asthma associated with neutrophil influx than in classical eosinophilic inflammation.

TNF-α

TNF-α is a pro-inflammatory cytokine principally produced by monocytes and macrophages. Antagonism of TNF-α by soluble receptors or neutralising antibodies has been strikingly effective in the therapy of rheumatoid arthritis and other inflammatory diseases (Ref. 145). In a mast-cell-dependent model of AAI, AHR, inflammation and Th2 cytokine production were markedly reduced in $TNF^{-/-}$ mice (Ref. 146). In severe clinical asthma, TNF was overexpressed, and a trial of soluble TNF receptor demonstrated beneficial effects on AHR, FEV_1 and quality-of-life score (Ref. 147).

Chemokines

Chemokines are a large family of cytokines with chemotactic activity. They are key regulators of

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leukocyte migration, both in homeostasis and in inflammation (Ref. 148). Much attention has been given to the possibility of manipulating the chemokine system in the treatment of asthma. The role of chemokines in asthma has been reviewed recently (Refs 149, 150) and is covered only briefly here. The complexity of the chemokine network had provided challenges in identifying suitable therapeutic targets. Many chemokines bind to multiple receptors, and many of the chemokine receptors bind multiple chemokines (Ref. 149). Despite this complexity, the chemokine receptor CCR3 is a potential target in asthma, because it is a key chemotactic receptor on eosinophils, binding the chemokines CCL5 (RANTES), CCL11 (eotaxin-1), CCL24 (eotaxin-2) and CCL26 (eotaxin-3) (Refs 151, 152). Knockout mice lacking CCR3 demonstrate marked reduction in AAI in asthma models, although effects on AHR have been variable (Refs 152, 153, 154). Recently, orally administered small-molecule CCR3 antagonists were shown to inhibit AAI in a mouse model (Ref. 155).

Further evidence for a role of CCR3 in AAI comes from studies on CXCL9 (MIG), CXCL10 (IP-10) and CXCL11 (I-TAC). These chemokines are agonists of the CXCR3 chemokine receptor and are induced by IFN-γ. In addition to binding to CXCR3, they function as receptor antagonists of CCR3, thereby preventing eosinophil migration (Refs 156, 157). These data are consistent with in vivo studies on CXCL9 and CXCL10, which inhibited airway eosinophil recruitment (Refs 158, 159), although expression of CXCL10 in the airways caused spontaneous AHR and airway eosinophilia (Ref. 160). The different findings on CXCL10 indicate the complexity of the chemokine network.

Other chemokine receptors have been identified as potential targets. A monoclonal antibody to CCR2 – a marker of macrophages, T cells, dendritic cells and neutrophils – was recently demonstrated to inhibit eosinophilic infiltration and AHR in AAI in cynomolgus monkeys (Ref. 161). CCR4 is another potential target, as IL-4-producing T cells in the blood and bronchoalveolar fluid of asthma patients express CCR3 and CCR4 (Ref. 162), and airway eosinophilia and AHR were reduced in mice lacking CCR4 (Ref. 163).

Given the importance of T cells to asthma, it is significant to note that airway epithelial cells produce several T cell chemokines. For example, the recruitment of CCR4-expressing Th2 $CD4^+$ cells to the allergic lung is facilitated by airway epithelial cell production of a CCR4 ligand, CCL17 (TARC) (Ref. 164). Ligation of CD40 on airway epithelium stimulates the production of CCL2 and CCL5 (Ref. 165), further illustrating the potential for cooperation between airway epithelial cells and the adaptive immune response in directing asthma. A recent study in mice lacking the cytokine TNF-related apoptosis-inducing ligand (TRAIL) demonstrated reduced AAI and AHR. The absence of TRAIL impaired production of CCL20, thereby inhibiting the homing of dendritic cells and T cells expressing CCR6, the receptor of CCL20, to the airways (Ref. 166).

Additional cytokines regulating AAI

Other cytokines have been shown to be involved in murine models and may have a role in clinical asthma. These include IL-25, which is also known as IL-17E because it is structurally a member of the IL-17 family. IL-25 is produced by Th2 cells and promotes airway inflammation and AHR in mice in an IL-13-dependent fashion (Ref. 167). The cytokine amphiregulin, a member of the epidermal growth factor family, is produced by activated mast cells and is associated with mucus production in asthmatic airways (Ref. 168). Considering the preferential expression of amphiregulin in Th2 rather than Th1 cells, and the impaired nematode clearance in amphiregulin-deficient mice (Ref. 169), amphiregulin may have an important role in regulating AAI. Another relevant cytokine is GM-CSF, which has a wide range of pro-inflammatory effects on granulocytes, macrophages and dendritic cells, including effects on eosinophils that overlap those of IL-5 (Ref. 170). Mice lacking functional GM-CSF genes had a marked reduction in bronchial eosinophilia and mucus production (Ref. 171).

It is important to note that AAI is a highly complex process, and that the activity of a vast array of cytokines and chemokines in addition to those described above is required for pathogenesis. Nevertheless, clinical experience with inhibition of TNF in rheumatoid arthritis (Ref. 145) indicates that a blockade of a single critical cytokine can have potent clinically useful anti-inflammatory effects.

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Concluding comments

AAI involves the interplay of multiple cell types and bioactive mediators, and is a key component of asthma pathology. Studies into the pathogenesis of AAI have informed clinical trials aimed at targeting specific components of the allergic response (Refs 88, 113, 116, 131, 132, 147). The variable success of these trials suggests that the immunopathogenesis of asthma is very complex, involving mechanisms in addition to those suggested by mouse models of AAI. It has been suggested that AAI is most important during the early stages of asthma, prior to the development of extensive tissue damage and remodelling. This suggests that clinical trials targeting Th2 immunity might be better directed at children, rather than the adult populations that have been tested to date (Ref. 172).

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References

1 Masoli, M. et al. (2004) The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 59, 469-478
2 Marks, G.B., Correll, P.K. and Williamson, M. (2005) Asthma in Australia 2005. Med J Aust 183, 445-446
3 von Hertzen, L. and Haahtela, T. (2005) Signs of reversing trends in prevalence of asthma. Allergy 60, 283-292
4 Weiss, K.B. and Sullivan, S.D. (2001) The health economics of asthma and rhinitis. I. Assessing the economic impact. J Allergy Clin Immunol 107, 3-8
5 Mallol, J. et al. (2008) Heightened bronchial hyperresponsiveness in the absence of heightened atopy in children with current wheezing and low income status. Thorax 63, 167-171
6 Wills-Karp, M. (1999) Immunologic basis of antigen-induced airway hyperresponsiveness. Annu Rev Immunol 17, 255-281
7 Douwes, J. et al. (2002) Non-eosinophilic asthma: importance and possible mechanisms. Thorax 57, 643-648
8 Zosky, G.R. and Sly, P.D. (2007) Animal models of asthma. Clin Exp Allergy 37, 973-988
9 Persson, C.G. (2002) Con: mice are not a good model of human airway disease. Am J Respir Crit Care Med 166, 6-7; discussion 8
10 Clark, K. et al. (2004) Eosinophil degranulation in the allergic lung of mice primarily occurs in the airway lumen. J Leukoc Biol 75, 1001-1009
11 Kumar, R.K. and Foster, P.S. (2002) Modeling allergic asthma in mice: pitfalls and opportunities. Am J Respir Cell Mol Biol 27, 267-272
12 Johnson, J.R. et al. (2004) Continuous exposure to house dust mite elicits chronic airway inflammation and structural remodeling. Am J Respir Crit Care Med 169, 378-385
13 Zosky, G.R. et al. (2008) Ovalbumin-sensitized mice are good models for airway hyperresponsiveness but not acute physiological responses to allergen inhalation. Clin Exp Allergy 38, 829-838
14 Gelfand, E.W. (2002) Pro: mice are a good model of human airway disease. Am J Respir Crit Care Med 166, 5-6; discussion 7-8
15 Gavett, S.H. et al. (1994) Depletion of murine CD4+ T lymphocytes prevents antigen-induced airway hyperreactivity and pulmonary eosinophilia. Am J Respir Cell Mol Biol 10, 587-593
16 Cohn, L., Elias, J.A. and Chupp, G.L. (2004) Asthma: mechanisms of disease persistence and progression. Annu Rev Immunol 22, 789-815
17 Robinson, D.S. et al. (1992) Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. N Engl J Med 326, 298-304
18 Abbas, A.K., Murphy, K.M. and Sher, A. (1996) Functional diversity of helper T lymphocytes. Nature 383, 787-793
19 Amsen, D. et al. (2004) Instruction of distinct CD4 T helper cell fates by different notch ligands on antigen-presenting cells. Cell 117, 515-526
20 Kaplan, M.H. et al. (1996) Stat6 is required for mediating responses to IL-4 and for development of Th2 cells. Immunity 4, 313-319
21 Kopf, M. et al. (1993) Disruption of the murine IL-4 gene blocks Th2 cytokine responses. Nature 362, 245-248
22 Akimoto, T. et al. (1998) Abrogation of bronchial eosinophilic inflammation and airway hyperreactivity in signal transducers and activators of transcription (STAT)6-deficient mice. J Exp Med 187, 1537-1542
23 Mathew, A. et al. (2001) Signal transducer and activator of transcription 6 controls chemokine production and T helper cell type 2 cell trafficking

Accession information: doi:10.1017/S1462399408000707; Vol. 10; e15; May 2008

in allergic pulmonary inflammation. J Exp Med 193, 1087-1096
24 Gernez, Y. et al. (2007) Altered phosphorylated signal transducer and activator of transcription profile of CD4+CD161+ T cells in asthma: modulation by allergic status and oral corticosteroids. J Allergy Clin Immunol 120, 1441-1448
25 Zheng, W. and Flavell, R.A. (1997) The transcription factor GATA-3 is necessary and sufficient for Th2 cytokine gene expression in CD4 T cells. Cell 89, 587-596
26 Ho, I.C., Lo, D. and Glimcher, L.H. (1998) c-maf promotes T helper cell type 2 (Th2) and attenuates Th1 differentiation by both interleukin 4-dependent and -independent mechanisms. J Exp Med 188, 1859-1866
27 Rengarajan, J., Tang, B. and Glimcher, L.H. (2002) NFATc2 and NFATc3 regulate T(H)2 differentiation and modulate TCR-responsiveness of naive T(H)cells. Nat Immunol 3, 48-54
28 Rincon, M. and Flavell, R.A. (1997) Transcription mediated by NFAT is highly inducible in effector CD4+ T helper 2 (Th2) cells but not in Th1 cells. Mol Cell Biol 17, 1522-1534
29 Masuda, A. et al. (2004) The interaction between GATA proteins and activator protein-1 promotes the transcription of IL-13 in mast cells. J Immunol 173, 5564-5573
30 Tu, L. et al. (2005) Notch signaling is an important regulator of type 2 immunity. J Exp Med 202, 1037-1042
31 Amsen, D. et al. (2007) Direct regulation of Gata3 expression determines the T helper differentiation potential of Notch. Immunity 27, 89-99
32 Kaplan, M.H. et al. (1996) Impaired IL-12 responses and enhanced development of Th2 cells in Stat4-deficient mice. Nature 382, 174-177
33 Seder, R.A. et al. (1993) Interleukin 12 acts directly on CD4+ T cells to enhance priming for interferon gamma production and diminishes interleukin 4 inhibition of such priming. Proc Natl Acad Sci U S A 90, 10188-10192
34 Szabo, S.J. et al. (2000) A novel transcription factor, T-bet, directs Th1 lineage commitment. Cell 100, 655-669
35 Usui, T. et al. (2006) T-bet regulates Th1 responses through essential effects on GATA-3 function rather than on IFNG gene acetylation and transcription. J Exp Med 203, 755-766
36 Finotto, S. et al. (2002) Development of spontaneous airway changes consistent with human asthma in mice lacking T-bet. Science 295, 336-338
37 Ko, F.W. et al. (2007) Decreased T-bet expression and changes in chemokine levels in adults with asthma. Clin Exp Immunol 147, 526-532
38 Bettelli, E., Korn, T. and Kuchroo, V.K. (2007) Th17: the third member of the effector T cell trilogy. Curr Opin Immunol 19, 652-657
39 Ivanov, II et al. (2006) The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. Cell 126, 1121-1133
40 Acosta-Rodriguez, E.V. et al. (2007) Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. Nat Immunol 8, 942-949
41 Veldhoen, M. et al. (2006) TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. Immunity 24, 179-189
42 Korn, T. et al. (2007) IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells. Nature 448, 484-487
43 Langrish, C.L. et al. (2005) IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. J Exp Med 201, 233-240
44 Wing, K., Fehervari, Z. and Sakaguchi, S. (2006) Emerging possibilities in the development and function of regulatory T cells. Int Immunol 18, 991-1000
45 Watanabe, N. et al. (2005) Hassall's corpuscles instruct dendritic cells to induce CD4+CD25+ regulatory T cells in human thymus. Nature 436, 1181-1185
46 Sakaguchi, S. (2004) Naturally arising CD4+ regulatory T cells for immunologic self-tolerance and negative control of immune responses. Annu Rev Immunol 22, 531-562
47 Seddiki, N. et al. (2006) Expression of interleukin (IL)-2 and IL-7 receptors discriminates between human regulatory and activated T cells. J Exp Med 203, 1693-1700
48 Kearley, J. et al. (2005) Resolution of airway inflammation and hyperreactivity after in vivo transfer of CD4+CD25+ regulatory T cells is interleukin 10 dependent. J Exp Med 202, 1539-1547
49 Lewkowich, I.P. et al. (2005) CD4+CD25+ T cells protect against experimentally induced asthma and alter pulmonary dendritic cell phenotype and function. J Exp Med 202, 1549-1561

Accession information: doi:10.1017/S1462399408000707; Vol. 10; e15; May 2008

50 Su, Y.C. et al. (2006) Cyclophosphamide augments inflammation by reducing immunosuppression in a mouse model of allergic airway disease. J Allergy Clin Immunol 117, 635-641
51 Akbari, O., DeKruyff, R.H. and Umetsu, D.T. (2001) Pulmonary dendritic cells producing IL-10 mediate tolerance induced by respiratory exposure to antigen. Nat Immunol 2, 725-731
52 Strickland, D.H. et al. (2006) Reversal of airway hyperresponsiveness by induction of airway mucosal CD4+CD25+ regulatory T cells. J Exp Med 203, 2649-2660
53 Ling, E.M. et al. (2004) Relation of CD4+CD25+ regulatory T-cell suppression of allergen-driven T-cell activation to atopic status and expression of allergic disease. Lancet 363, 608-615
54 Akdis, M. et al. (2004) Immune Responses in Healthy and Allergic Individuals Are Characterized by a Fine Balance between Allergen-specific T Regulatory 1 and T Helper 2 Cells. J Exp Med 1, 1
55 Kamradt, T., Goggel, R. and Erb, K.J. (2005) Induction, exacerbation and inhibition of allergic and autoimmune diseases by infection. Trends Immunol 26, 260-267
56 Yazdanbakhsh, M., van den Biggelaar, A. and Maizels, R.M. (2001) Th2 responses without atopy: immunoregulation in chronic helminth infections and reduced allergic disease. Trends Immunol 22, 372-377
57 Yazdanbakhsh, M., Kremsner, P.G. and van Ree, R. (2002) Allergy, parasites, and the hygiene hypothesis. Science 296, 490-494
58 Wilson, M.S. et al. (2005) Suppression of allergic airway inflammation by helminth-induced regulatory T cells. J Exp Med 202, 1199-1212
59 Wohlleben, G. et al. (2004) Helminth infection modulates the development of allergen-induced airway inflammation. Int Immunol 16, 585-596
60 Stumbles, P.A. et al. (1998) Resting respiratory tract dendritic cells preferentially stimulate T helper cell type 2 (Th2) responses and require obligatory cytokine signals for induction of Th1 immunity. J Exp Med 188, 2019-2031
61 Lambrecht, B.N. et al. (2000) Myeloid dendritic cells induce Th2 responses to inhaled antigen, leading to eosinophilic airway inflammation. J Clin Invest 106, 551-559
62 van Rijt, L.S. et al. (2004) Essential role of dendritic cell CD80/CD86 costimulation in the induction, but not reactivation, of TH2 effector responses in a mouse model of asthma. J Allergy Clin Immunol 114, 166-173
63 Radhakrishnan, S. et al. (2005) Dendritic cells activated by cross-linking B7-DC (PD-L2) block inflammatory airway disease. J Allergy Clin Immunol 116, 668-674
64 Genovese, M.C. et al. (2005) Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med 353, 1114-1123
65 Wang, Y.H. et al. (2006) Maintenance and polarization of human TH2 central memory T cells by thymic stromal lymphopoietin-activated dendritic cells. Immunity 24, 827-838
66 Al-Shami, A. et al. (2004) A role for thymic stromal lymphopoietin in CD4(+) T cell development. J Exp Med 200, 159-168
67 Al-Shami, A. et al. (2005) A role for TSLP in the development of inflammation in an asthma model. J Exp Med 202, 829-839
68 Ying, S. et al. (2005) Thymic stromal lymphopoietin expression is increased in asthmatic airways and correlates with expression of Th2-attracting chemokines and disease severity. J Immunol 174, 8183-8190
69 Rimoldi, M. et al. (2005) Intestinal immune homeostasis is regulated by the crosstalk between epithelial cells and dendritic cells. Nat Immunol 6, 507-514
70 Rothenberg, M.E. and Hogan, S.P. (2006) The eosinophil. Annu Rev Immunol 24, 147-174
71 Eum, S.Y. et al. (1995) Eosinophil recruitment into the respiratory epithelium following antigenic challenge in hyper-IgE mice is accompanied by interleukin 5-dependent bronchial hyperresponsiveness. Proc Natl Acad Sci U S A 92, 12290-12294
72 Foster, P.S. et al. (1996) Interleukin 5 deficiency abolishes eosinophilia, airways hyperreactivity, and lung damage in a mouse asthma model. J Exp Med 183, 195-201
73 Corry, D.B. et al. (1996) Interleukin 4, but not interleukin 5 or eosinophils, is required in a murine model of acute airway hyperreactivity. J Exp Med 183, 109-117
74 Tournoy, K.G. et al. (2000) Airway eosinophilia is not a requirement for allergen-induced airway hyperresponsiveness. Clin Exp Allergy 30, 79-85
75 Wilder, J.A. et al. (1999) Dissociation of airway hyperresponsiveness from immunoglobulin E and airway eosinophilia in a murine model of allergic asthma. Am J Respir Cell Mol Biol 20, 1326-1334
76 Humbles, A.A. et al. (2004) A critical role for eosinophils in allergic airways remodeling. Science 305, 1776-1779

Accession information: doi:10.1017/S1462399408000707; Vol. 10; e15; May 2008

77 Lee, J.J. et al. (2004) Defining a link with asthma in mice congenitally deficient in eosinophils. Science 305, 1773-1776
78 Marshall, J.S. and Jawdat, D.M. (2004) Mast cells in innate immunity. J Allergy Clin Immunol 114, 21-27
79 Kawakami, T. and Galli, S.J. (2002) Regulation of mast-cell and basophil function and survival by IgE. Nat Rev Immunol 2, 773-786
80 Lorentz, A. et al. (2000) Human intestinal mast cells are capable of producing different cytokine profiles: role of IgE receptor cross-linking and IL-4. J Immunol 164, 43-48
81 Bradding, P. et al. (1994) Interleukin-4, -5, and -6 and tumor necrosis factor-alpha in normal and asthmatic airways: evidence for the human mast cell as a source of these cytokines. Am J Respir Cell Mol Biol 10, 471-480
82 Bradding, P., Walls, A.F. and Holgate, S.T. (2006) The role of the mast cell in the pathophysiology of asthma. J Allergy Clin Immunol 117, 1277-1284
83 Nigo, Y.I. et al. (2006) Regulation of allergic airway inflammation through Toll-like receptor 4-mediated modification of mast cell function. Proc Natl Acad Sci U S A 103, 2286-2291
84 Williams, C.M. and Galli, S.J. (2000) Mast cells can amplify airway reactivity and features of chronic inflammation in an asthma model in mice. J Exp Med 192, 455-462
85 Yu, M. et al. (2006) Mast cells can promote the development of multiple features of chronic asthma in mice. J Clin Invest 16, 1633-1641
86 Schulman, E.S. (2001) Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. Am J Respir Crit Care Med 164, S6-11
87 Fahy, J.V. et al. (1997) The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. Am J Respir Crit Care Med 155, 1828-1834
88 Djukanovic, R. et al. (2004) Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. Am J Respir Crit Care Med 170, 583-593
89 Wu, A.C. et al. (2007) Cost-effectiveness of omalizumab in adults with severe asthma: results from the Asthma Policy Model. J Allergy Clin Immunol 120, 1146-1152
90 Knight, D.A. and Holgate, S.T. (2003) The airway epithelium: structural and functional properties in health and disease. Respirology 8, 432-446
91 Komiya, A. et al. (2003) Concerted expression of eotaxin-1, eotaxin-2, and eotaxin-3 in human bronchial epithelial cells. Cell Immunol 225, 91-100
92 Hahn, C. et al. (2006) Airway epithelial cells produce neurotrophins and promote the survival of eosinophils during allergic airway inflammation. J Allergy Clin Immunol 117, 787-794
93 Braun, A. et al. (1998) Role of nerve growth factor in a mouse model of allergic airway inflammation and asthma. Eur J Immunol 28, 3240-3251
94 Asokananthan, N. et al. (2002) Activation of protease-activated receptor (PAR)-1, PAR-2, and PAR-4 stimulates IL-6, IL-8, and prostaglandin E2 release from human respiratory epithelial cells. J Immunol 168, 3577-3585
95 King, C. et al. (1998) Dust mite proteolytic allergens induce cytokine release from cultured airway epithelium. J Immunol 161, 3645-3651
96 Lordan, J.L. et al. (2002) Cooperative effects of Th2 cytokines and allergen on normal and asthmatic bronchial epithelial cells. J Immunol 169, 407-414
97 Pichavant, M. et al. (2005) Asthmatic bronchial epithelium activated by the proteolytic allergen Der p 1 increases selective dendritic cell recruitment. J Allergy Clin Immunol 115, 771-778
98 Boldogh, I. et al. (2005) ROS generated by pollen NADPH oxidase provide a signal that augments antigen-induced allergic airway inflammation. J Clin Invest 115, 2169-2179
99 Hassim, Z., Maronese, S.E. and Kumar, R.K. (1998) Injury to murine airway epithelial cells by pollen enzymes. Thorax 53, 368-371
100 Broide, D.H. et al. (2005) Allergen-induced peribronchial fibrosis and mucus production mediated by IkappaB kinase beta-dependent genes in airway epithelium. Proc Natl Acad Sci U S A 102, 17723-17728
101 Kuperman, D.A. et al. (2002) Direct effects of interleukin-13 on epithelial cells cause airway hyperreactivity and mucus overproduction in asthma. Nat Med 8, 885-889
102 Madan, T. et al. (2001) Surfactant proteins A and D protect mice against pulmonary hypersensitivity induced by Aspergillus fumigatus antigens and allergens. J Clin Invest 107, 467-475
103 Shum, B.O. et al. (2006) The adipocyte fatty acid-binding protein aP2 is required in allergic airway inflammation. J Clin Invest 116, 2183-2192
104 Lloyd, C.M. et al. (2001) Mouse models of allergic airway disease. Adv Immunol 77, 263-295
105 Moffatt, J.D. (2005) What targets have knockouts revealed in asthma? Pharmacol Ther 107, 343-357

Accession information: doi:10.1017/S1462399408000707; Vol. 10; e15; May 2008

106 Zimmermann, N. et al. (2003) Chemokines in asthma: cooperative interaction between chemokines and IL-13. J Allergy Clin Immunol 111, 227-242
107 Le Gros, G. et al. (1990) Generation of interleukin 4 (IL-4)-producing cells in vivo and in vitro: IL-2 and IL-4 are required for in vitro generation of IL-4-producing cells. J Exp Med 172, 921-929
108 Coffman, R.L. et al. (1986) B cell stimulatory factor-1 enhances the IgE response of lipopolysaccharide-activated B cells. J Immunol 136, 4538-4541
109 Kelly-Welch, A.E. et al. (2003) Interleukin-4 and interleukin-13 signaling connections maps. Science 300, 1527-1528
110 Cohn, L. et al. (1997) Induction of airway mucus production By T helper 2 (Th2) cells: a critical role for interleukin 4 in cell recruitment but not mucus production. J Exp Med 186, 1737-1747
111 Brusselle, G. et al. (1995) Allergen-induced airway inflammation and bronchial responsiveness in wild-type and interleukin-4-deficient mice. Am J Respir Cell Mol Biol 12, 254-259
112 Hogan, S.P. et al. (1998) A novel T cell-regulated mechanism modulating allergen-induced airways hyperreactivity in BALB/c mice independently of IL-4 and IL-5. J Immunol 161, 1501-1509
113 Borish, L.C. et al. (2001) Efficacy of soluble IL-4 receptor for the treatment of adults with asthma. J Allergy Clin Immunol 107, 963-970
114 Walker, C. et al. (1992) Allergic and nonallergic asthmatics have distinct patterns of T-cell activation and cytokine production in peripheral blood and bronchoalveolar lavage. Am Rev Respir Dis 146, 109-115
115 Johansson, A.K. et al. (2004) Allergen-induced traffic of bone marrow eosinophils, neutrophils and lymphocytes to airways. Eur J Immunol 34, 3135-3145
116 Leckie, M.J. et al. (2000) Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. Lancet 356, 2144-2148
117 Flood-Page, P. et al. (2007) A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. Am J Respir Crit Care Med 176, 1062-1071
118 Kips, J.C. et al. (2003) Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. Am J Respir Crit Care Med 167, 1655-1659
119 Flood-Page, P.T. et al. (2003) Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. Am J Respir Crit Care Med 167, 199-204
120 Soussi-Gounni, A., Kontolemos, M. and Hamid, Q. (2001) Role of IL-9 in the pathophysiology of allergic diseases. J Allergy Clin Immunol 107, 575-582
121 Temann, U.A., Ray, P. and Flavell, R.A. (2002) Pulmonary overexpression of IL-9 induces Th2 cytokine expression, leading to immune pathology. J Clin Invest 109, 29-39
122 Steenwinckel, V. et al. (2007) IL-13 mediates in vivo IL-9 activities on lung epithelial cells but not on hematopoietic cells. J Immunol 178, 3244-3251
123 Cheng, G. et al. (2002) Anti-interleukin-9 antibody treatment inhibits airway inflammation and hyperreactivity in mouse asthma model. Am J Respir Crit Care Med 166, 409-416
124 Kung, T.T. et al. (2001) Effect of anti-mIL-9 antibody on the development of pulmonary inflammation and airway hyperresponsiveness in allergic mice. Am J Respir Cell Mol Biol 25, 600-605
125 McMillan, S.J. et al. (2002) The absence of interleukin 9 does not affect the development of allergen-induced pulmonary inflammation nor airway hyperreactivity. J Exp Med 195, 51-57
126 Mueller, T.D. et al. (2002) Structure, binding, and antagonists in the IL-4/IL-13 receptor system. Biochim Biophys Acta 1592, 237-250
127 Wills-Karp, M. et al. (1998) Interleukin-13: central mediator of allergic asthma. Science 282, 2258-2261
128 Wills-Karp, M. (2004) Interleukin-13 in asthma pathogenesis. Immunol Rev 202, 175-190
129 Grunig, G. et al. (1998) Requirement for IL-13 independently of IL-4 in experimental asthma. Science 282, 2261-2263
130 Wilson, M.S. et al. (2007) IL-13Ralpha2 and IL-10 coordinately suppress airway inflammation, airway-hyperreactivity, and fibrosis in mice. J Clin Invest 117, 2941-2951
131 Wenzel, S. et al. (2007) Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies. Lancet 370, 1422-1431
132 Bryan, S.A. et al. (2000) Effects of recombinant human interleukin-12 on eosinophils, airway hyper-responsiveness, and the late asthmatic response. Lancet 356, 2149-2153
133 Cho, S.H. et al. (2005) Increased interleukin-4, interleukin-5, and interferon-gamma in airway CD4+ and CD8+ T cells in atopic asthma. Am J Respir Crit Care Med 171, 224-230
134 Krug, N. et al. (1996) T-cell cytokine profile evaluated at the single cell level in BAL and blood in allergic asthma. Am J Respir Cell Mol Biol 14, 319-326

Accession information: doi:10.1017/S1462399408000707; Vol. 10; e15; May 2008

135 Huang, T.J. et al. (2001) Allergen-specific Th1 cells counteract efferent Th2 cell-dependent bronchial hyperresponsiveness and eosinophilic inflammation partly via IFN-gamma. J Immunol 166, 207-217
136 Hansen, G. et al. (1999) Allergen-specific Th1 cells fail to counterbalance Th2 cell-induced airway hyperreactivity but cause severe airway inflammation. J Clin Invest 103, 175-183
137 Randolph, D.A. et al. (1999) Cooperation between Th1 and Th2 cells in a murine model of eosinophilic airway inflammation. J Clin Invest 104, 1021-1029
138 Hessel, E.M. et al. (1997) Development of airway hyperresponsiveness is dependent on interferon-gamma and independent of eosinophil infiltration. Am J Respir Cell Mol Biol 16, 325-334
139 Kumar, R.K. et al. (2004) Effects of anticytokine therapy in a mouse model of chronic asthma. Am J Respir Crit Care Med 170, 1043-1048
140 Bullens, D.M. et al. (2006) IL-17 mRNA in sputum of asthmatic patients: linking T cell driven inflammation and granulocytic influx? Respir Res 7, 135
141 Henness, S. et al. (2006) IL-17A acts via p38 MAPK to increase stability of TNF-alpha-induced IL-8 mRNA in human ASM. Am J Physiol Lung Cell Mol Physiol 290, L1283-1290
142 Rahman, M.S. et al. (2006) IL-17A induces eotaxin-1/CC chemokine ligand 11 expression in human airway smooth muscle cells: role of MAPK (Erk1/2, JNK, and p38) pathways. J Immunol 177, 4064-4071
143 Hellings, P.W. et al. (2003) Interleukin-17 orchestrates the granulocyte influx into airways after allergen inhalation in a mouse model of allergic asthma. Am J Respir Cell Mol Biol 28, 42-50
144 Schnyder-Candrian, S. et al. (2006) Interleukin-17 is a negative regulator of established allergic asthma. J Exp Med 203, 2715-2725
145 Feldmann, M. and Maini, R.N. (2001) Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? Annu Rev Immunol 19, 163-196
146 Nakae, S. et al. (2007) TNF can contribute to multiple features of ovalbumin-induced allergic inflammation of the airways in mice. J Allergy Clin Immunol 119, 680-686
147 Berry, M.A. et al. (2006) Evidence of a role of tumor necrosis factor alpha in refractory asthma. N Engl J Med 354, 697-708
148 Rot, A. and von Andrian, U.H. (2004) Chemokines in innate and adaptive host defense: basic chemokinese grammar for immune cells. Annu Rev Immunol 22, 891-928
149 Palmqvist, C., Wardlaw, A.J. and Bradding, P. (2007) Chemokines and their receptors as potential targets for the treatment of asthma. Br J Pharmacol 151, 725-736
150 Smit, J.J. and Lukacs, N.W. (2006) A closer look at chemokines and their role in asthmatic responses. Eur J Pharmacol 533, 277-288
151 Heath, H. et al. (1997) Chemokine receptor usage by human eosinophils. The importance of CCR3 demonstrated using an antagonistic monoclonal antibody. J Clin Invest 99, 178-184
152 Pope, S.M. et al. (2005) The eotaxin chemokines and CCR3 are fundamental regulators of allergen-induced pulmonary eosinophilia. J Immunol 175, 5341-5350
153 Humbles, A.A. et al. (2002) The murine CCR3 receptor regulates both the role of eosinophils and mast cells in allergen-induced airway inflammation and hyperresponsiveness. Proc Natl Acad Sci U S A 99, 1479-1484
154 Ma, W. et al. (2002) CCR3 is essential for skin eosinophilia and airway hyperresponsiveness in a murine model of allergic skin inflammation. J Clin Invest 109, 621-628
155 Das, A.M. et al. (2006) Selective inhibition of eosinophil influx into the lung by small molecule CCR3 antagonists in mouse models of allergic inflammation. J Pharmacol Exp Ther 318, 411-417
156 Loetscher, P. et al. (2001) The ligands of CXC chemokine receptor 3, I-TAC, Mig, and IP10, are natural antagonists for CCR3. J Biol Chem 276, 2986-2991
157 Xanthou, G. et al. (2003) CCR3 functional responses are regulated by both CXCR3 and its ligands CXCL9, CXCL10 and CXCL11. Eur J Immunol 33, 2241-2250
158 Fulkerson, P.C. et al. (2004) Negative regulation of eosinophil recruitment to the lung by the chemokine monokine induced by IFN-gamma (Mig, CXCL9). Proc Natl Acad Sci U S A 101, 1987-1992
159 Thomas, M.S., Kunkel, S.L. and Lukacs, N.W. (2002) Differential role of IFN-gamma-inducible protein 10 kDa in a cockroach antigen-induced model of allergic airway hyperreactivity: systemic versus local effects. J Immunol 169, 7045-7053
160 Medoff, B.D. et al. (2002) IFN-gamma-inducible protein 10 (CXCL10) contributes to airway hyperreactivity and airway inflammation in a mouse model of asthma. J Immunol 168, 5278-5286
161 Mellado, M. et al. (2008) Chemokine receptor 2 blockade prevents asthma in a cynomolgus monkey model. J Pharmacol Exp Ther 324, 769-775

Accession information: doi:10.1017/S1462399408000707; Vol. 10; e15; May 2008

162 Morgan, A.J. et al. (2005) IL-4-expressing bronchoalveolar T cells from asthmatic and healthy subjects preferentially express CCR 3 and CCR 4. J Allergy Clin Immunol 116, 594-600
163 Schuh, J.M. et al. (2002) Airway hyperresponsiveness, but not airway remodeling, is attenuated during chronic pulmonary allergic responses to Aspergillus in CCR4-/- mice. FASEB J 16, 1313-1315
164 Sekiya, T. et al. (2000) Inducible expression of a Th2-type CC chemokine thymus- and activation-regulated chemokine by human bronchial epithelial cells. J Immunol 165, 2205-2213
165 Propst, S.M. et al. (2000) Proinflammatory and Th2-derived cytokines modulate CD40-mediated expression of inflammatory mediators in airway epithelia: implications for the role of epithelial CD40 in airway inflammation. J Immunol 165, 2214-2221
166 Weckmann, M. et al. (2007) Critical link between TRAIL and CCL20 for the activation of T(H)2 cells and the expression of allergic airway disease. Nat Med 13, 1308-1315
167 Sharkhuu, T. et al. (2006) Mechanism of interleukin-25 (IL-17E)-induced pulmonary inflammation and airways hyper-reactivity. Clin Exp Allergy 36, 1575-1583
168 Okumura, S. et al. (2005) FcepsilonRI-mediated amphiregulin production by human mast cells increases mucin gene expression in epithelial cells. J Allergy Clin Immunol 115, 272-279
169 Zaiss, D.M. et al. (2006) Amphiregulin, a TH2 cytokine enhancing resistance to nematodes. Science 314, 1746
170 Ritz, S.A. et al. (2002) On the generation of allergic airway diseases: from GM-CSF to Kyoto. Trends Immunol 23, 396-402
171 Su, Y.C. et al. (2008) Granulocyte-macrophage colony-stimulating factor is required for bronchial eosinophilia in a murine model of allergic airway inflammation. J Immunol 180, 2600-2607
172 Holt, P.G. et al. (2004) Drug development strategies for asthma: in search of a new paradigm. Nat Immunol 5, 695-698

Further reading, resources and contacts

Publications

Kay, A.B. (2005) The role of eosinophils in the pathogenesis of asthma. Trends Mol Med 11, 148-152
This review provides further reading on one of the most controversial topics in asthma pathogenesis.

Holgate, S.T. and Polosa, R. (2006) The mechanisms, diagnosis, and management of severe asthma in adults. Lancet 368, 780-793
This review provides an up-to-date coverage of clinical issues affecting the most severely affected 5–10% of asthma patients, who have the most to gain from novel biological therapies.

Casale, T.B. and Stokes, J.R. (2008) Immunomodulators for allergic respiratory disorders. J Allergy Clin Immunol 121, 288-296
This recent article summarises data on clinical trials with novel therapeutic agents.

Harnett, M.M. and Harnett, W. Therapeutic immunomodulators from nematode parasites. Expert Rev Mol Med (in press)
This forthcoming article in *Expert Reviews in Molecular Medicine* reviews the relationship between parasite infection and allergic diseases.

Websites

The American Academy of Allergy, Asthma and Immunology website offers extensive information for patients, medical professionals, its members and the media:

http://www.aaaai.org/

The Australasian Society for Clinical Immunology and Allergy website provides a variety of position papers and other useful information for health professionals and patients:

http://www.allergy.org.au/

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Features associated with this article

Figure
Figure 1. Cytokine regulation of allergic asthma.

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