Molecular mechanisms in allergy and clinical immunology

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Activity Objectives

(a) To understand the role of the T cell in the asthma process.

(b) To obtain a general understanding of molecular mechanisms involved in T_H2 cell function.

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The role of T lymphocytes in the pathogenesis of asthma

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There is considerable evidence to support a role for T cells in asthma, particularly the involvement of T_H2 cells both in atopic allergic asthma and in nonatopic and occupational asthma. There might also be a minor contribution from T_C2 $CD8^+$ T cells. Several T_H2 cytokines have the potential to modulate airway inflammation, particularly IL-13, which induces airway hyperresponsiveness independently of IgE and eosinophilia in animal models. The identification of transcription factors controlling T_H1 and T_H2 development further support the T_H2 hypothesis because GATA3 is overexpressed and T-bet is underexpressed in the asthmatic airway. Specific T cell–directed immunotherapy might allow induction, modulation, or both of T-cell responses, and elucidation of the mechanisms of regulatory T cells might allow further optimization of immunotherapy. Recent advances in our understanding of dendritic cell function in directing T-cell responses might uncover further therapeutic targets. The efficacy of cyclosporin A and anti-CD4 treatment in patients with chronic severe asthma argues for continued T-cell involvement, but whether remodeling contributes to pathology inaccessible to anti-inflammatory treatment or T-cell immunotherapy will be an important future question. (J Allergy Clin Immunol 2003;111:450-63.)

Key words: *Asthma, T cells, allergy, T_H2 cytokines, chemokines, antigen-presenting cells, immunotherapy, T regulatory cells, atopy, airway hyperresponsiveness, remodeling*

In the late 1980s, it was suggested that in ongoing asthma there were "chronically activated helper T cells driven by (allergen, and) as yet undetermined antigens (possibly viral) (which)… may perpetuate the inflammatory response in and around the bronchi… (through)… the release of T–cell-derived-lymphokines."[1] The T-cell hypothesis of asthma developed from studies of late asthmatic reactions (LARs)[2] and acute severe asthma (status asthmaticus)[3] and was supported by the observation that there was a T_H2-type T-cell cytokine profile in this disease.[4] A critical role for T_H2 cells in asthma is now widely accepted.[5]

Asthma is defined as a chronic inflammatory condition, with characteristic eosinophilic inflammation and airway

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Abbreviations used
AHR: Airway hyperresponsiveness
BAL: Bronchoalveolar lavage
DC: Dendritic cell
ICOS: Inducible costimulator
LAR: Late asthmatic reaction
MDC: Monocyte-derived chemokine
NF-κB: Nuclear factor κB
STAT: Signal transducer and activator of transcription
TARC: Thymus- and activation-regulated chemokine

remodeling.[5,6] However, the relationship between T-cell activation and immunopathology and the clinical features of airway hyperresponsiveness (AHR), variable airway narrowing and cough, are still not fully understood. Similarly, the links between T_H2- and IgE-mediated atopy, allergen challenge models in experimental animals and human subjects, and day-to-day asthma of varying severity remain to be fully defined. This review will focus on more recent data on the role of T cells in asthma, particularly new insights into the control of T-cell function, how T-cell activation contributes to clinical features, and the potential for manipulation of the immune response in treatment of this common and chronic disorder.

T CELLS AND T_H2 CYTOKINES IN ASTHMA

It is well known that allergen-specific IgE synthesis is T cell dependent through cognate activation of B lymphocytes and T cell–derived cytokines, such as IL-4 and IL-13.[7] Thus in atopic asthma and allergic rhinitis allergen processing and presentation to allergen-specific T cells through antigen-presenting cells is a key initiation step. Growing interest in the role of the T cell in asthma arose from the concept that, in addition to participating in IgE synthesis, T-cell products might also have direct effects on the airways through the recruitment of inflammatory cells, particularly eosinophils. A number of studies showed evidence for $CD4^+$ T-cell activation in the peripheral blood of asthmatic patients during exacerbations.[2] Sampling of the airways either with bronchial biopsy or bronchoalveolar lavage (BAL) revealed T cells with features of activation.[8-10] In some studies T-cell activation could be related both to measures of asthma severity, such as the degree of airway narrowing or AHR, and to the bronchial eosinophil response.[9,11,12] Similarly, after the description of the T_H2/T_H1 dichotomy, $mRNA^+$ cells for the signature T_H2 cytokines IL-4 and IL-5 were detected in airway samples from atopic asthmatic patients.[13] This linked IgE synthesis through IL-4 and eosinophilic airway inflammation through IL-5, together with IL-3 and GM-CSF.[1,14,15] In addition, a number of investigators have isolated allergen-specific T-cell lines and clones from the BAL fluid of asthmatic patients.[16,17]

THE ASTHMA PHENOTYPES

The contribution of allergy across the spectrum of asthma has always been vigorously debated. One study showed that only about half of asthma is atopic,[18] and therefore the following is an important question: What is the role of T cells and, more particularly, T_H2 cells in the nonatopic (intrinsic) form of the disease, as well as in occupational asthma and acute exacerbations, in which viruses often appear to be the triggering factor. Bronchial biopsy specimens from nonatopic patients and patients with occupational asthma have revealed remarkable similarities to those from patients with atopic asthma, at least at the level of immunopathology.[19-21] Thus eosinophil infiltration and cells bearing markers of T-cell activation, such as CD25, were present in increased numbers in bronchial biopsy specimens from all 3 forms of disease. Similarly, the cytokine profile in the airways of patients with nonatopic asthma also showed prominence of IL-4, IL-5, and IL-13, with no increase in IFN-γ compared with that seen in nonasthmatic control volunteers. More recent data have demonstrated evidence for local IgE synthesis in the bronchial mucosa of nonatopic asthmatic patients, supporting a T_H2- and IgE-mediated immunopathologic process,[22] despite the absence of specific serum IgE or positive skin prick test responses. Interestingly, it has been suggested that self-antigens might drive the T_H2 response in nonatopic asthma.[23] Further work will be required to understand the role of IgE in this disease, including how it might be triggered. Similarly, some occupational asthma studies involving low-molecular-weight agents, such as toluene diisocyanate, suggest T_H2-type cytokine production in the airway,[20,24] although it is of note that the IgE dependence of occupational asthma is not always demonstrated.

Initial studies of airway biopsy specimens were restricted to patients with mild asthma with well-preserved lung function, although there was also evidence of T-cell infiltration and activation in postmortem airway tissue from asthmatic patients dying both from asthma and from other causes,[25] as well as BAL and transbronchial biopsy studies in patients with more severe asthma.[26,27] In some patients there is marked eosinophilic inflammation of the small airways together with T-cell activation, but others show sparse inflammatory changes or neutrophilic inflammation. Whether such findings reflect different pathologic mechanisms or the effect of treatment (often with high-dose inhaled or oral corticosteroids) remains to be established.

EFFECTOR MECHANISMS: HOW DO T CELLS CAUSE ASTHMA?

Over the past few years, a working hypothesis has been that T_H2 cytokines contribute to asthma pathology through IgE synthesis, maturation and activation of mast cells and basophils (and thus acute asthma), and IL-5–mediated eosinophil infiltration, leading to epithelial damage and AHR.[5] Some studies also showed T_H1 cytokines in serum and BAL fluid from asthmatic patients,[28] particularly during exacerbations, although most studies confirm T_H2 predominance in stable disease. It also soon became apparent that mast cells,

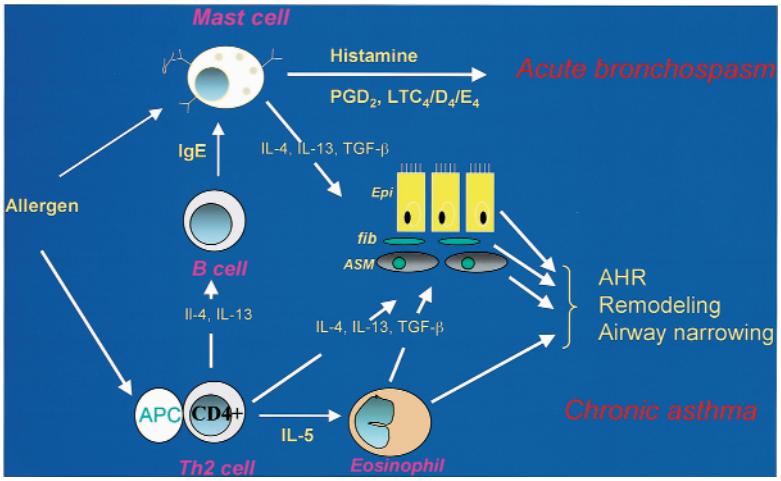

FIG 1. An overview scheme of possible interactions among mast cells, T_H2 cells, eosinophils, airway remodeling, AHR, acute bronchospasm, and chronic asthma. The interaction of allergen with specific IgE passively absorbed to mast cells leads to the noncytolytic, energy-dependent release of histamine and lipid mediators from mast cells. This might account for the acute airway narrowing (bronchospasm) that occurs within minutes of exposure to specific allergen. Antigen-presenting cells in the airways, particularly DCs, process and present allergenic peptides to CD4 cells in an MHC class II restriction fashion. T_H2 CD4 cells elaborate IL-4 and IL-13, which are involved in IgE production by B cells; transforming growth factor β, together with IL-4 and IL-13, have direct effects on fibroblasts, epithelial cells, and airway smooth muscle, which in turn leads to the release of growth factors and fibrogenic factors involved in remodeling, AHR, and airway narrowing. IL-5 derived from T_H2 cells and other cells facilitates the development and activation of eosinophils. Eosinophils have a direct effect on airway narrowing through the release of basic proteins and lipid mediators and indirectly influence airway remodeling through the release of transforming growth factor β, IL-4, and IL-13. These cytokines are also elaborated from mast cells, and this mechanism might also amplify the chronic asthma process. *LT,* Leukotriene; *Epi,* epithelial cells; *fib,* fibroblasts; *ASM,* airway smooth muscle; *APC,* antigen-presenting cell; *TGF,* transforming growth factor.

basophils, and eosinophils were themselves potential sources of T_H2-type cytokines.[29,30] Indeed, immunohistochemical staining for cytokines in bronchial biopsy specimens suggested that these cytokines localized mainly to non-T cells.[31] However, these findings likely reflect storage of cytokines in mast cells, eosinophils, and basophils because mRNA for IL-4 and IL-5 localized predominantly to T cells, with minor contributions from mast cells, basophils, and eosinophils.[13]

Data from animal studies (see below) suggested that AHR could be initiated by T cells through mechanisms that were not dependent on either IgE or eosinophils. This might also be the case for human asthma because direct interaction of T cells and airway smooth muscle is suggested, and both IL-5 and IL-13 have been shown to have the ability to increase smooth muscle contractility to acetylcholine in vitro.[32,33]

ARE T CELLS REQUIRED TO PERPETUATE ASTHMA?

Much attention has been focused on airway remodeling in asthma.[34] This encompasses changes in the epithelium, subepithelial basement membrane deposition of collagen and other extracellular matrix proteins, increased vascularity, and smooth muscle hypertrophy and hyperplasia. It has been suggested that the smooth muscle changes alone are sufficient to sustain AHR.[35] Bronchial mucosa biopsy specimens of asthmatic patients compared with those from patients with eosinophilic bronchitis (which is characterized by cough without reversible airway narrowing or AHR) showed no differences in mucosal eosinophil or T-cell infiltration. However, mast cell infiltration of smooth muscle was seen in the asthmatic patients but not in the patients with eosinophilic bronchitis, and it was therefore suggested that AHR and airway narrowing in asthma were more related to smooth muscle and mast cell interaction than the eosinophil–T cell axis.[36] These findings raise the question of whether T cells are important in sustaining chronic asthma or in initiating the pathologic process. Data discussed below showing that T cell–directed therapy is effective in chronic asthma argue for a continued role, although it is equally true that the persistent AHR and incomplete abolition of symptoms after broad anti-inflammatory treatment (eg, with corticosteroids) might result from structural airway changes. The development of specific T cell–directed therapy and better animal models of chronic airway inflammation might provide further information in this important area. An overview scheme of possible interactions between mast cells, T_H2 cells, eosinophils, airway remodeling, AHR, acute bronchospasm, and chronic asthma is shown in Fig 1.

TABLE I. T cell–related cytokines in asthma

Cytokine	T_H1/T_H2/Treg associated	Actions	Producer cells in human patients	Animal models of airway inflammation	Human asthma
IL-2	T_H1	T-cell growth factor	T_H1 cells, Eos	Decreased	Increased
IL-3	T_H1/T_H2	Differentiation and activation of Eos, Neu, Baso, MC	T_H1/T_H2 cells, Eos, MC, Baso, Mac/Mono, Fib	Increased: blocking decreases eosinophilia	Increased
IL-4	T_H2	B-cell switch to IgE synthesis, MC development, Eos and Baso activation, mucus, secretion, favors T_H2 production, increased Endo VCAM expression	T_H2 cells, Eos, MC, Baso	Increased; blocking decreases AHR (but some residual)	Increased; soluble IL-4 receptor had some steroid-sparing effect
IL-5	T_H2	Eos, Baso differentiation, maturation, and activation	T_H2, Eos, MC, Baso	Increased; knockout or blocking decreases Eos and AHR	Increased; antibody decreased eosinophils but not AHR
IL-6	T_H1/T_H2	T- and B-cell growth factor, cofactor for IgE synthesis	T_H1/T_H2 cells, Mac, Endo	Transgene showed increased AHR and inflammation, knockout less	Increased (in severe asthma)
IL-8		Neu activation-chemotaxis; weak Eos chemotaxis	Endo, Epi, Mac, Fib, T cells	IL-8 receptor knockout decreased AHR and neutrophils	Increased
IL-9	T_H2	MC and Eos development, AHR, mucus secretion	T_H2 cells, Eos, MC, Baso	Transgene had Eos, AHR, and mucus; knockout no effect	Increased
IL-10	Treg	Suppresses T_H1/T_H2 function, Eos/MC/Baso activation, favors Treg production, B-cell switch to IgG4	T cells, Mac	Adenoviral transfer decreased inflammation	Decreased/increased
IL-11		AHR, eosinophilia, mucus hypersecretion, airway remodeling	Fib, Mac, Endo, Epi	Transgene had AHR and changes of remodeling	Increased
IL-12	T_H1	Favors T_H1 production, inhibits IgE synthesis	Mac, B cells	Exogenous IL-12 blocked eosinophils and AHR	Decreased; exogenous IL-12 decreased Eos but not AHR
IL-13	T_H2	MC development, B-cell switch to IgE production, eosinophilia, AHR, mucus hypersecretion	T_H2 cells, Eos, MC, Baso	Increased; soluble IL-13 receptor blocked AHR but not Eos or IgE	Increased
IL-15	T_H1	T-cell growth factor; expands Treg	Many non–T cells	?	Decreased
IL-16		Chemoattractant for CD4 cells, Mono, Eos	$CD8^+$, MC, Eos	Increased	Increased
IL-17		Induces inflammatory cytokine production by Fib, Mac, Epi, Endo	CD4 memory cells	Provokes airway neutrophilia	Increased
IL-18	T_H1	Induces IFN-γ production by T cells, NK cells; favors T_H1 expansion	Mac	Knockout increased Eos and AHR, exogenous IL-18 (with IL-12) decreased AHR and Eos	Reduced
IL-23	T_H1	Cofactor for T_H1 development, activates DCs	Various hemopoietic cells	Not studied	Not studied
IL-25	T_H2	Favors T_H2 development and IL-4, IL-5, and IL-13 production	T_H2 cells	Adenoviral transfer induces T_H2 cytokines, Eos, AHR, and mucus	Not studied
IL-27	T_H1	Favors T_H1 expansion	APC	Not studied	Not studied
GM-CSF	T_H1/T_H2	Differentiation and activation of Eos, Neu, Easo, MC	T_H1/T_H2, Mac, Eos, MC, Baso, Fib, Epi, Endo	Increased; transgene has airway inflammation	Increased
TNF-α		Activation of Endo and Epi	Mac, NK cells, T cells	Increased	Increased
TGF-β	Treg	Suppresses T_H1/T_H2 function, favors Treg induction, cofactor for IgA secretion, fibrosis	Eos, MC, Baso, T cells, Mono, Mac	Increased	Increased
IFN-γ	T_H1	Inhibits IgE synthesis, inhibits T_H2 induction, activates Eos and Mac	T_H1 cells, NK cells	Decreased	Increased in viral infection and exacerbations

Treg, T-cell regulatory cell; *Eos,* eosinophil; *Neu,* neutrophil; *Baso,* basophil; *MC,* mast cell; *Mac,* macrophage; *Mono,* monocyte; *Fib,* fibroblast; *VCAM,* vascular cell adhesion molecule; *Endo,* endothelial cell; *Epi,* epithelial cell; *APC,* antigen-presenting cell; *TGF,* transforming growth factor.

NEW CYTOKINES, INTRACELLULAR CONTROLLERS OF T-CELL FUNCTION AND ANIMAL MODELS: WHAT DO THEY TELL US ABOUT ASTHMA?

In the 10 years since the description of T_H2 cytokines in asthma, an array of novel cytokines has been described, and our understanding of the molecular control of T-cell activation and differentiation has improved. Studies from animal models and some human data support the relevance of some of these factors in human asthma.

T cell–derived cytokines and cytokines that act on T cells

Many more cytokines with potential relevance to asthma have been described. IL-25 acts in T_H2 differentiation; IL-9, IL-11, IL-13, IL-16, and IL-17 have been linked to asthma; and IL-12, IL-18, IL-23, and IL-27 are involved in T_H1 development and IFN-γ production, which might be deficient in patients with asthma (Table I). Mouse models of asthma usually involve relatively short-term sensitization and inhaled challenge protocols more akin to allergen challenge than chronic asthma, and results vary with the strain studied.[37] Nonetheless, these have given considerable insight into the potential for T cells and cytokines to act in the airway.

Most data come from removing the cytokine by means of gene disruption (knockouts), the use of blocking antibodies, or overexpression by transgenes. These models support the T_H2 hypothesis in that adoptive transfer of differentiated T_H2 cells can induce airway eosinophilia and AHR on inhaled challenge (whereas T_H1 cells do not), and IL-4 and IL-5 were both implicated in airway eosinophilia and AHR for challenge in different knockout and antibody studies.[37-39] IL-9 was implicated in AHR initially from studies linking strain differences in baseline AHR with IL-9 expression and increased AHR and eosinophilia in IL-9 transgenics,[40,41] although response to airway challenge was not reduced in sensitized IL-9 knockout animals.[42] Like IL-9, transgenic expression of IL-11 and IL-13 in the airway of mice was sufficient to induce eosinophilia, AHR, hypersecretion, and variable changes similar to those caused by remodeling.[43,44] Transgenic expression of IL-11 in the airway leads to lymphocytic infiltration and remodeling yet inhibits the T_H2 response to inhaled antigen.[45] IL-11 has also been reported to favor T_H2 polarization of naive T cells.[46] Thus IL-11 can be associated with T_H2 responses and chronic repair and remodeling.

IL-4 and IL-5 were implicated in different mouse models of asthma.[38,39] Interestingly, a soluble IL-13 receptor could reverse AHR in a mouse model without affecting serum IgE or airway eosinophilia.[47,48] Similarly, Hogan et al[49] reported that blocking IL-4 in an IL5 gene–deleted mouse did not completely abrogate AHR or airway eosinophilia in response to inhaled challenge and that the residual AHR was T-cell dependent.[49] This group has also suggested that non–IgE- and non–eosinophil-induced T-cell dependent AHR was not a feature of mice deficient for IL-5, eotaxin, and IL-13.[50]

IL-16 is a $CD4^+$ lymphocyte chemoattractant,[51] whereas IL-17 is a T cell–derived cytokine that can induce fibroblast production of proinflammatory cytokines, including GM-CSF.[52] IL-25 is a more recently characterized cytokine with homology to IL-17 and drives T_H2 IL-4, IL-5, and IL-13 production in murine T cells.[53] Adenoviral transfer of IL-25 into the lungs of mice causes eosinophilic inflammation, epithelial changes, mucus hypersecretion, and AHR.[54] All of these cytokines (except IL-25) have been reported to be overrepresented in the airways of asthmatic subjects when compared with levels in nonasthmatic control volunteers, and IL-11 was detected in patients with severe asthma, in whom it might act in remodeling.[55-58]

Because the array of T-cell cytokines with potential to contribute to asthma pathology has expanded, this might, in turn, explain the disappointing results of single cytokine-directed therapy for asthma. Cytokines involved in T_H1 development and phenotype expression have also been studied in animal models and human asthma. Thus IL-12 and IL-18 (with IL-12) have the potential to reduce airway inflammation to inhaled challenge after T_H2 sensitization, and AHR and eosinophilia was increased in IL-18–deficient animals compared with in wild-type control animals.[59-61] Similarly, it has been suggested that IL-12 and IL-18 are deficient in human airway samples in asthma, and this might relate to similar relative underexpression of T-bet.[62-64] To date, IL-23 and IL-27 studies in models of human asthma have not been reported.

Controls of T-cell cytokine production

A number of transcription factors and signaling molecules have been shown to have potential roles in animal models, including c-maf, nuclear factor κB (NF-κB), nuclear factor of activated T cells, and signal transducer and activator of transcription 6 (STAT6).[64] At least 2 transcription factors with the potential to control T_H1 or T_H2 development have been described. GATA3 is implicated in T_H2 development in mouse and human T cells and is an important controller of the *IL5* gene locus.[65] In mouse models blocking GATA3 with a dominant negative construct or antisense DNA could prevent T_H2 cytokine activation, eosinophilia, and AHR in challenge models.[66,67] Further knockout mice with a p50 NF-κB defect failed to mount a GATA3 or T_H2 response in an antigen sensitization and airway challenge model, suggesting that NF-κB might control GATA3 expression in developing T_H2 cells.[68] Numbers of GATA3-expressing cells were increased in bronchial biopsy specimens from asthmatic patients, supporting this as a target for control of T_H2 cells in asthma.[69] Christodoulopoulos et al[70] have examined other transcription factors and showed increased expression of cells bearing GATA3, c-maf (a transcription factor for IL-4), and STAT6 (which transduces signals for IL-4 and IL-13) in bronchial biopsy specimens from both atopic and nonatopic asthmatic patients compared with in specimens from control subjects. However, STAT6 expression was less prominent in nonatopic asthma, suggesting IL-4 signaling might play a less important role.

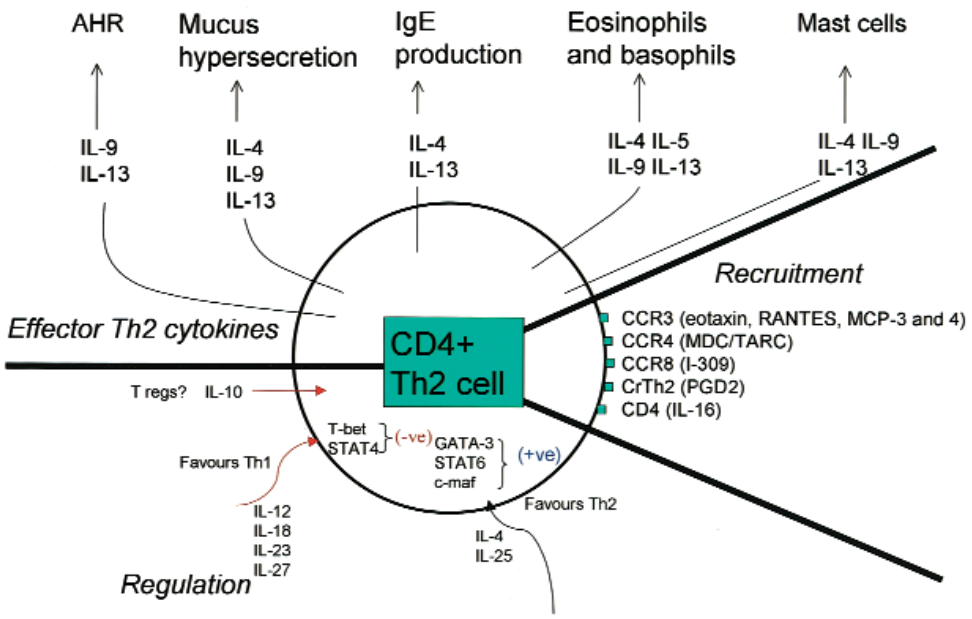

FIG 2. A diagrammatic representation of factors influencing the regulation, recruitment, and effector functions of T_H2 cells. The recruitment of CD4 T_H2 cells is dependent on the expression of receptors for CC chemokines and CD4. T_H2 cells express CCR3, CCR4, CCR8, and CRT_H2. Their respective ligands are shown. IL-16, the ligand for CD4, also serves as a specific chemoattractant. The regulation of elaboration of effector T_H2 cytokines is dependent on cytokines that favor T_H2 (IL-4 and IL-25) and its respective transcription factors, GATA-3, STAT6, and c-maf, whereas negative regulation occurs through cytokines that favor T_H1 (ie, IL-12, IL-18, IL-23, and IL-27). These T_H1 transcription factors include T-bet and STAT4. T regulatory cells elaborating IL-10 might also be involved in the inhibition of effector functions of $CD4^+$ T_H2 cells. The effector T_H cytokines display considerable pleotropism. For example, in addition to IgE production, IL-4 is involved in mucus hypersecretion, eosinophil and basophil recruitment, and mast cell differentiation. *APC,* Antigen-presenting cells; *MCP,* monocyte chemotactic protein; *T regs,* T-cell regulatory cells.

Recently, T-bet was described as a controller of T_H1 development and is shown to direct IFN-γ production and IL-12 receptor β2 expression.[71,72] Finotto et al[73] described reduced numbers of cells staining for T-bet in bronchial biopsy specimens from asthmatic patients and spontaneous AHR in mice deficient in T-bet. These findings again suggest that asthma is associated with reduced airway T_H1 cells, and the authors speculate that a defect in T_H1 development through a deficiency in T-bet might predispose to T_H2 responses. It is of note that T_H2 cytokines in human T cells appear to be coordinately regulated[74] through the activity of a number of these transcription factors, and it might thus be possible to target a range of cytokines through therapy directed an interfering with this process. However, this remains hypothetical at present. A diagrammatic representation of factors that influence the regulation, recruitment, and effector functions of T_H2 cells is shown in Fig 2.

PROVOKED ASTHMA UNDER CONTROLLED CLINICAL CONDITIONS

Inhaled allergen challenge of sensitized atopic asthmatic patients has been used for many years as a model of asthma to study both the early and late reaction.[75] Although the early reaction is thought be IgE and mast cell dependent, the cause and significance of the LAR and associated increased AHR is less certain. Although cutaneous late responses could be induced by passive transfer of IgE and rechallenge,[76] the skin and lung response are associated with eosinophil and T-cell infiltration, and studies at 24 hours after challenge show increases in T-cell activation and T_H2 cytokine expression, which can be correlated with the preceding airway narrowing during the LAR.[77-80] This model is essentially similar to that used in mouse models, except that there is background chronic inflammation in the airway in human asthmatic patients. How it relates to chronic asthma is uncertain, but like the mouse models, human allergen challenge has proved instructive. T-cell dependence in mouse models could be directly demonstrated by means of anti-CD4 antibody depletion of T cells.[49] Data to support a role of T cells in the human LAR came from inhibition of the LAR with cyclosporin A, a drug that targets T-cell activation through nuclear factor of activated T cells–driven IL-2 production and also inhibits T-cell IL-5 production.[81] However, cyclosporin A was also reported to act on mast cell and basophil degranulation.[82,83] In a further study, bronchoscopy revealed that inhibition of the LAR by cyclosporin A was associated with accelerated apoptosis of BAL fluid $CD3^+$ cells, as well as decreases in eosinophils and IL-5.[84] This provided indirect evidence that cyclosporin A is effective in this human model of asthmatic allergic

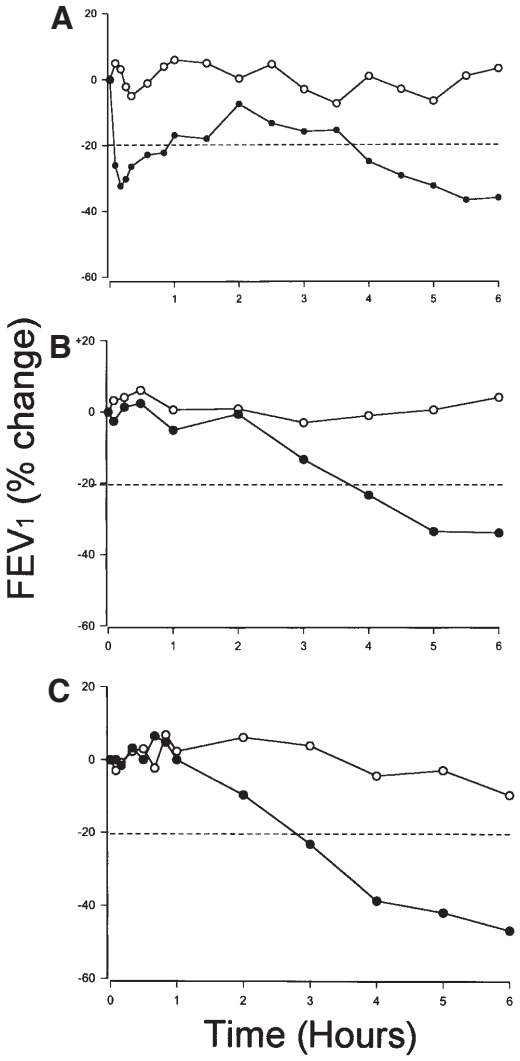

FIG 3. Different patterns of airway response after challenge with whole allergen or T-cell peptides. In approximately 50% of allergic asthmatic patients, inhalation of whole-allergen extract results in a biphasic reduction in FEV_1. The early asthmatic reaction occurs within the first hour. The LAR is initiated between 2 and 4 hours and peaks at 6 to 9 hours. Challenge of allergic asthmatic patients through either the intradermal route or the inhaled route results in an isolated LAR. **A,** Whole cat dander. An asthmatic patient with cat allergy was challenged with either nebulized saline *(open circles)* or nebulized whole cat dander allergen extract *(filled circles)* through the inhaled route. In contrast to saline, challenge with allergen resulted in both early asthmatic response and LAR. A reduction of 20% in FEV_1 was arbitrarily considered significant to allow for normal variation in airway caliber in an asthmatic subject *(dotted line)*. **B,** Intradermal peptides. An asthmatic patient with cat allergy was challenged with either saline or a mixture of overlapping peptides spanning the majority of the Fel d 1 molecule. Administration of saline or peptide was through intradermal injection in the volar aspect of the forearm. In contrast to the saline control, injection of peptides resulted in an isolated LAR. **C,** Peptides by inhalation. An asthmatic patient with cat allergy was challenged with either saline or a mixture of overlapping peptides spanning the majority of the Fel d 1 molecule. Administration of saline or peptide was through inhalation of nebulized material (particle size of approximately 5 μm). In contrast to challenge with saline, peptides induced an isolated LAR.

inflammation principally through its effects on the T cells and associated eosinophil events, rather than actions on mast cells and basophils.

Studies from our own group have shown that direct T-cell activation through intradermal injection of short peptides derived from the cat allergen Fel d 1 could induce an isolated LAR in asthmatic patients with cat allergy.[85,86] Peptides were shown to be capable of binding to MHC class II molecules but did not cross-link IgE in a basophil histamine release assay. The peptide-induced LAR was MHC restricted in that it only occurred in those individuals with MHC class II able to bind the injected peptides, further supporting a role for T cells in the observed response. The mechanism of LARs induced by means of intradermal injection of peptide (without reaction in the skin) is uncertain. Unlike LAR induced after inhalation of whole allergen, bronchoscopic analysis of peptide-induced LAR showed no evidence of eosinophil infiltration or T-cell activation in the airway, with no change in IL-5, IL-13, histamine, or leukotriene levels detected in paired BAL samples from peptide- and diluent-challenged subjects. This might be because the LAR was elicited through the circulation rather than through the airway or that there is direct T cell–mediated smooth muscle contraction. We have recently shown that inhaled peptide can also induce LAR in asthmatic patients with cat allergy.[87] Reactions induced by inhaled peptides were accompanied by sputum eosinophilia, suggesting that changes in inflammatory mediators and mucosa infiltration of effector cells is only detectable by means of bronchoscopy after topical challenge with peptides. The potential for such peptides in therapy is discussed below. Examples of the different patterns of airway response after challenge with whole allergen or T-cell peptides is shown in Fig 3.

ACTIVATION OF T CELLS IN ASTHMA: ANTIGEN-PRESENTING CELLS

In addition to presentation of antigen peptide in the context of MHC, T-cell activation requires costimulation and additional signals.[88] A number of factors might influence antigen-presenting cells, and dendritic cells (DCs) are plastic in their ability to drive T-cell responses to T_H1- or T_H2-type responses.[89] DC function is partially controlled by signals from the innate immune system, in part through toll-like receptors, through control of IL-12 and IL-10 production. Different costimulation molecules and other factors might also influence DC function. Recent data suggest that inducible costimulator (ICOS) costimulation in the mouse lung favors an IL-10–producing T cell with potential suppressive activity.[90] However, other mouse data suggest that ICOS favors T_H2 responses, and blocking ICOS can reduce AHR and eosinophilia in an animal model of allergen challenge.[91] The role of ICOS in human asthma remains to be defined. We have shown that human BAL T cells can be activated with allergen to proliferate and secrete IL-5 and that this was CD86 dependent. Furthermore, adherent cells

from BAL fluid obtained from patients with asthma (predominantly alveolar macrophages) were as effective at presenting antigen to T cells as blood monocytes.[92] Histamine has also been shown to affect DC function, driving DCs to favor T_H2 cell expansion through H1 and H2 receptors.[93] This could clearly be relevant to asthma. Whether targeting of costimulation or DC function can be sufficiently specific to be useful for asthma therapy remains to be established.

CD8 T CELLS AND γδ CELLS

There are several reports that suggest that $CD8^+$ cells might participate in the asthma process. An early study involving BAL after allergen inhalational challenge suggested that $CD8^+$ cells might be involved in the regulation of the expression of the LAR because there were relative increases in $OKT8^+$ lavage cells in early-phase compared with late-phase responders.[2] On the other hand, several studies have indicated that $CD8^+$ cells might be proinflammatory in the airways. In both atopic and nonatopic asthmatic patients, mRNA for IL-4 and IL-5 colocalized predominantly to $CD4^+$ cells but also to $CD8^+$ T cells,[13] findings in agreement with those of Till et al,[16] who found that $CD8^+$, as well as $CD4^+$, T-cell lines from BAL fluid from asthmatic patients elaborated the IL-5 protein. Cho et al[94] were able to demonstrate increased numbers of IL-4 protein/$CD8^+$ cells in blood from atopic patients with mild asthma. All these observations are compatible with the concept of a population of $CD8^+$ T cytotoxic type 2 (T_C2) lymphocytes. Some studies have suggested increases in $CD8^+$ cells in occupational asthma,[95] and in a mouse model it was shown that virus-specific $CD8^+$ cells switch to IL-5 production and induce airway eosinophilia.[96] This raises the possibility that in asthma certain viruses or chemical haptens might modify intrinsic antigens, which in turn are targeted by $CD8^+$ cytotoxic cells.

Although some animal data suggest that γδ T cells might be important in models of asthma or allergic sensitization,[97-99] there is conflicting evidence to support a role in human asthma.[100-102]

HOMING OF T CELLS TO THE AIRWAY IN ASTHMA

It has been established for some time that T cells use adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), during trafficking to the airway, but there is increasing interest in the role of specific chemokines in either tissue-directed T-cell homing or in recruitment of different T-cell subtypes. Most of the current data come from mouse models or human allergen challenge studies. In vitro mouse and human T_H2 cells are polarized to preferentially express CCR3, CCR4, and CCR8 and interact with their ligands: eotaxin, monocyte-derived chemokine (MDC), thymus- and activation-regulated chemokine (TARC), and I-309/TCA-3. In experiments involving adoptive transfer of polarized T-cell receptor transgenic T_H2 cells to recipient mice followed by inhaled challenge, early infiltrating T cells (first challenge) were predominantly $CCR3^+$, and influx was reduced by blocking antibodies to eotaxin, whereas later T-cell infiltration was of $CCR4^+$ T cells and was blocked by antibody to MDC.[103] However, the effects of CCR3, CCR4, and CCR8 knockout in mice are complex, and lack of these receptors does not totally prevent T_H2 cell infiltration and AHR after antigen sensitization and inhaled challenge. In the CCR3 knockout mice there was a reduction in eosinophil trafficking to the lung after allergen challenge but an increase in intraepithelial mast cells and an overall increase in airway hyperresponsiveness to challenge.[104] In the CCR4 knockout mice there was no effect on eosinophils or AHR in an ovalbumin antigen challenge model,[105] but inflammatory response and AHR were reduced in an *Aspergillus* species model.[106] For CCR8, the knockout mouse showed diminished eosinophil recruitment in response to ovalbumin or cockroach allergen sensitization and airway challenge, but AHR was not measured, and there was no change in T cell numbers.[107] Some of these changes might relate to the finding that CCR8 is expressed by murine eosinophils.[108] In human patients Panina-Bordignon et al[109] observed that virtually all T cells from endobronchial biopsy specimens from asthmatic patients taken 24 hours after allergen challenge expressed IL-4 and CCR4.[109] CCR8 was coexpressed with CCR4 on 28% of the T cells, whereas CCR3 was associated with eosinophils but not on T cells. Interestingly, expression of the CCR4-specific ligands MDC and TARC was strongly upregulated on airway epithelial cells on allergen challenge, suggesting an involvement of this receptor-ligand axis in the regulation of lymphocyte recruitment into the asthmatic bronchi. In contrast to asthma, T cells infiltrating the airways of patients with chronic obstructive pulmonary disease and pulmonary sarcoidosis produce IFN-γ and express high levels of CXCR3, while lacking CCR4 and CCR8 expression. These data supported a role of CCR4, its ligands MDC and TARC, and CCR8 in the pathogenesis of allergen-induced late asthma and a role for T cells in LARs. However, Campbell et al[110] examined BAL T cells from asthmatic patients compared with those from nonasthmatic control subjects and showed no differences (although the numbers were small) in the expression of CCR5 and CXCR3, with only low expression of CCR4. Such differences might result from analysis of allergen challenge versus baseline asthma, and further studies are required. Small-molecule antagonists of CCR3 and other chemokine receptors should be available for study in human patients in the near future.

T CELLS AND TREATMENT OF ASTHMA

Corticosteroids

Inhaled corticosteroids are the mainstay of asthma management, and these agents are extremely effective

in vitro as inhibitors of T-cell activation and cytokine production.[111] There are many studies showing a reduction in T-cell activation and cytokine expression in the airways of asthmatic patients after steroid treatment.[112,113] It is of interest that patients with corticosteroid-resistant asthma did not have reduced IL-5 levels in airway biopsy specimens after treatment with oral prednisolone.[114] The mechanism is unclear, but the T cell can be rendered steroid resistant in vitro by IL-2 and IL-4, and such patients fail to suppress T-cell activation markers in vivo after corticosteroid treatment and show abnormalities in T-cell transcription factor expression (AP-1, STAT5, and NF-κB), all of which suggests that this might be a T-cell defect.[115-117]

Cyclosporin A

Further support for the T-cell hypothesis of asthma was obtained from controlled clinical trials of cyclosporin A in patients with chronic asthma. In a group of patients with severe steroid-dependent asthma, treatment over a 12-week period with cyclosporin A at low dosage ($5 mg \cdot kg^{-1} \cdot d^{-1}$) was associated with improvement in lung function and a reduction in the numbers of disease exacerbations requiring an increase in corticosteroid dosage.[118] Reductions in the concentrations of serum IL-2 receptor after treatment with cyclosporin A were also observed. Two further studies have shown a corticosteroid-sparing effect of cyclosporin A in patients with steroid-dependent asthma.[119,120] Both showed improvements in lung function despite the reduction in corticosteroid dose, although in one patient this improvement was small.

More direct evidence of a role for T cells in the pathogenesis of chronic asthma was described by Kon et al,[121] who treated patients with severe corticosteroid-dependent asthma with a single infusion of a chimeric (primatized) mAb to human CD4. Subjects were treated in 3 separate dose groups in addition to a placebo arm. Patients receiving a single infusion of 3.0 mg/kg displayed a significant change in the morning and evening peak expiratory flow rates, with a trend toward an improvement in symptom scores. Taken together, these studies, in which T lymphocytes, particularly $CD4^+$ T lymphocytes, were targeted in allergic asthma, provides support for a significant role of these cells in the pathogenesis of asthma.

Studies with mAbs or receptor fusion proteins to block individual T cell–derived cytokines have been disappointing. Although our recent findings suggest that anti-IL-5 does not completely deplete airway eosinophils,[122] the lack of clinical efficacy of this treatment argues against a major direct effect of IL-5 on airway smooth muscle as an important contributor to AHR.[123] Some effects of a soluble IL-4 receptor have been reported in a protocol of steroid withdrawal in patients with mild asthma.[124,125] Human studies on IL-13 might be of interest, but, as stated, targeting single T-cell cytokines seems unlikely to be very effective.

ANTIGEN-DIRECTED TARGETING OF T CELLS AND REGULATORY T CELLS: THE FUTURE FOR ASTHMA THERAPY?

Allergen injection immunotherapy has long been used for the treatment of allergic asthma in many countries (although not in the United Kingdom). Current evidence suggests that immunotherapy modulates the T-cell response to allergen, either through immune deviation to a T_H1 response or through induction of a modified T_H2 or regulatory T-cell response with high IL-10 secretion.[126] IL-10 inhibits T-cell activation and cytokine secretion and switches B cells from IgE to IgG4 production.[127] Whole-allergen immunotherapy has modest effects in asthma compared with corticosteroids,[128] possibly because of dose limitation because of the potential for anaphylaxis caused by IgE cross-linking. We have focused our own efforts on attempts to produce a safe immunotherapeutic for allergic asthma by using MHC class II–restricted peptide fragments of allergen that inactivate T cells but do not cross-link IgE.

Previous studies demonstrated that peripheral T-cell tolerance could be induced in naive and primed mice by means of subcutaneous injection of peptides from the major cat allergen Fel d 1.[129] Subsequently, Norman et al[130] and others[131-133] treated patients with cat allergy by means of subcutaneous injection of 2 peptides (termed IPC1 and IPC2) that spanned a large proportion of chain 1 of Fel d 1. Although in some studies IPC1 and IPC2 were efficacious at high doses, their administration was associated with allergic symptoms that occurred between 10 minutes and 6 hours after subcutaneous injection. Because of their length (27 amino acids), the IPC1/IPC2-induced immediate reactions might have been the result of IgE cross-linking. For this reason, we subsequently synthesized 3 Fel d 1 chain 1 peptides of relatively small size (16/17 residues) to enable them to be presented to T cells in the absence of antigen processing and without cross-linking allergen-specific IgE.[85,86] The peptides stimulated in vitro proliferative responses in PBMCs from the majority of allergic and nonallergic individuals but displayed virtually no histamine-releasing activity from sensitized blood basophils, even at doses of greater than 100 μg/mL. As indicated earlier, intradermal administration of these peptides resulted in the induction of isolated LARs in certain individuals. Reactions were both dose dependent and MHC restricted, supporting the hypothesis that bronchoconstriction occurred as a result of direct and transient T-cell activation by the peptides.

Several studies in mice have shown that the development of T-cell tolerance in vivo is preceded by transient T-cell activation. Webb et al[134] reported that the clonal elimination of $V\beta_6+$ cells responding to a superantigen was preceded by marked expansion of these cells, whereas Vidard et al[135] found that before the establishment of specific T-cell tolerance to ovalbumin, T cells displayed transient responsiveness and synthesized IL-2 on anti-

genic stimulation in vitro. Similar findings were reported by Hoyne et al[136] by using an immunodominant peptide derived from house dust mite. In this model a strong, transient, T-cell $CD4^+$ response in vitro preceded the development of tolerance in vivo. Tsitoura et al[137] observed transient T-cell activation and production of T_H1 and T_H2 cytokines after tolerogenic intranasal administration of ovalbumin.

Rechallenge of asthmatic subjects with Fel d 1 peptides through the intradermal route resulted in reduction or abrogation of the isolated LAR in those individuals in whom such reactions occurred after initial challenge.[85,138,139]

Additionally, the magnitude of both early-phase and late-phase skin reactions to whole allergen challenge were also reduced, together with a reduction of proinflammatory immunologic parameters and an increase in the immunomodulatory cytokine IL-10.[139] Müller et al[140] observed similar changes in immunologic parameters after treating patients with bee venom allergy with peptides from phospholipase A_2.

Analysis of the extent of reduction in the magnitude of peptide-induced LARs and the interval between the first and second challenge with peptides demonstrated a window of optimal tolerance induction that appeared when injections were administered between approximately 2 weeks and 2 months apart. One implication of this observation is that the ability of peptides to activate a memory T-cell response that manifests itself as an isolated LAR in certain individuals and the ability to induce hyporesponsiveness in the allergen-specific T-cell compartment are unlikely to be linked temporally. Furthermore, reductions in early-phase and late-phase skin reactions to whole allergen challenge were observed with equal frequency and magnitude in those subjects who experienced an LAR and those who did not.

Thus it appears likely that the induction of transient T-cell activation and induction of hyporesponsiveness in this clinical model are separate events. Whether these can be separated and whether this treatment can reduce AHR and symptoms in asthma is the subject of ongoing work. Also of relevance for the future of immunotherapy is whether specific immunotherapy can be used to prevent asthma: certainly initial data are promising.[141]

There is much current interest in regulatory T cells. A number of such suppressive T-cell subsets have been described in mice and human patients, including naturally occurring $CD4^+CD25^+$ T cells, IL-10–producing T cells, and T_R1 cells.[142] Whether such cells can be induced therapeutically in asthma remains to be established, although, as discussed above, this is one possible mechanism of immunotherapy (both with peptides and whole-allergen extracts). One type of regulatory T cell was induced by a combination of corticosteroids and vitamin D3,[143] and corticosteroids increase IL-10 both in vitro and in vivo in asthma.[144,145] Thus it might be possible to manipulate long-lasting regulatory T-cell responses by pharmacologic means in asthma or to use drugs as adjuvants for immunotherapy.

CONCLUSIONS

There is now considerable evidence for the role of T cells in asthma. The hypothesis has generated a number of potential avenues for future therapy. Important remaining questions include the following:

- Will direct targeting of T cells, such as through peptide therapy, be effective for chronic asthma, or does airway remodeling preclude major responses to T cell–directed treatment?
- What drives the T-cell response in nonallergic intrinsic asthma?
- Are non-T_H2 products important in T cell–dependent airway narrowing?
- What controls the activation of airway T cells in atopic nonasthmatic patients and healthy individuals?
- Can treatments be developed that target multiple cytokines yet remain more specific than corticosteroids?
- What chemokines and receptors are important in T-cell recruitment and retention in the asthmatic airway?

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A. Barry Kay and Mark Larché are cofounders of an Imperial College spinout company, Circassia Ltd, whose aim was to develop MHC-based T-cell vaccines for treatment of allergic disease. Circassia Ltd is now a wholly owned subsidiary of Powderject Pharmaceuticals. A. Barry Kay and Mark Larché hold stock in and have consultancy agreements with Powderject Pharmaceuticals.

Douglas S. Robinson has no significant relationships to disclose.