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Cellular and molecular regulation of eosinophil trafficking to the lung

SIMON P HOGAN, ARNE W MOULD, JANINE M YOUNG, MARC E ROTHENBERG, ALISTAIR J RAMSAY, KLAUS MATTHAEI, IAN G YOUNG and PAUL S FOSTER

Divisions of Biochemistry and Molecular Biology and Division of Immunology and Cell Biology, John Curtin School of Medical Research, Australian National University, Acton, Australian Capital Territory, Australia and Division of Pulmonary Medicine, Allergy, and Clinical Immunology, Department of Pediatrics, Childrens Hospital, Medical Center, Cincinnati, Ohio, USA

Summary Airway inflammation is central to the pathogenesis of allergic asthma, and molecules that mediate this process obviously represent targets for therapy. In the present article, we discuss our experiments, which point to CD4+ T cells and IL-5-driven eosinophilia as potential targets for the relief of bronchial hyperactivity in late-phase asthma.

Key words: CD4+ T lymphocytes and eosinophils, eotaxin, interleukin-4, interleukin-5.

Introduction

In asthma, airway CD4+ Th2-type lymphocytes, mast cells and eosinophils appear to be the primary effector cells that underlie the clinical manifestations of disease. The cellular and molecular mechanisms involved in the recruitment of these inflammatory cells from the blood to sites of inflammation are complex, but cellular migration appears to be modulated by two fundamental processes: cell-adhesion systems located in the vascular endothelium and signals elicited through cytokine and chemokine (chemoattractant cytokines) receptors. Cell-adhesion and cytokine signalling systems form networks that are elegantly coordinated to promote cellular extravasation and localization to the site of inflammation. At the initiation of inflammation cytokines and chemokines play key roles in propagating the inflammatory response by eliciting signals that activate adhesion systems, induce the secretion of other cytokines/chemokines from the vascular bed and promote chemotaxis. The type of cytokines produced in response to a particular inflammatory stimulus is intimately involved in directing the immune response by promoting the selective mobilization, attachment and recruitment of specific leucocyte subsets to the site of provocation.

In asthma the inflammatory response appears to be predominantly driven by the Th2-type cytokines, in particular IL-4 and IL-5 secreted from allergen-specific CD4+ T cells. The Th2 cytokines may also be derived from activated mast cells and eosinophils. These cytokines, in association with specific adhesion molecules and other inflammatory molecules (e.g. chemokines, lipid mediators and prostaglandins) provide the basis of the molecular network that regulates the trafficking of leucocytes to the asthmatic lung. Whereas these cells and the individual mediators they release may contribute to a complex inflammatory cascade, their individual roles in the events that initiate the morphological and functional changes of the asthmatic lung are unknown.

In the present review we describe the contribution of IL-4, IgE and CD4+ Th2 cells and IL-5-regulated eosinophilic inflammation to the molecular and cellular mechanisms underlying the pathogenesis of allergic airways inflammation. We also describe the relationship between IL-5 and the newly identified chemokine, eotaxin, in the regulation of eosinophil trafficking to the lung. Investigations were performed in a mouse model of allergic airways disease that mimics certain phenotypic characteristics of late-phase asthmatic responses. Although animal models are only representative of the immunopathological process underlying asthma, they do provide important insights into the potential contribution of individual inflammatory cells and molecules to the pathogenesis of this disease, which, in turn, allows for the identification of key targets for potential therapeutic intervention.

Key cytokines and cells involved in regulating allergic airway inflammation

The accumulation and/or activation of inflammatory cells during an asthmatic response may be initiated and partially
sustained by cytokines released at sites of antigen provocation (such as the airway epithelium and from antigen-presenting cells) and from T cells and mast cells after activation by specific antigens. Interleukin-5 is highly potent and extremely rapid in inducing pulmonary and intradermal eosinophil recruitment (recently, eotaxin-2 has been identified). Investigations in guinea-pigs and mice suggest that Th2-type cytokines (IL-3, -4, -5, -10, -13 and granulocyte macrophage colony stimulating factor (GM-CSF)) play central roles in the asthmatic response by regulating the production of IgE, the effector function of mast cells and eosinophils, and by promoting transendothelial cell migration. In particular, IL-4 is thought to be a critical factor for the regulation of T cell commitment to the CD4+ Th2 phenotype and is known to regulate IgE production by B cells and mast cell function. In addition, IL-4 also has potential roles in regulating the inflammatory response to recall antigens and in the production of the eosinophil-specific chemoattractant, eotaxin. In conjunction with other Th2-type cytokines, as well as IL-1β and tumour necrosis factor, IL-4 may also regulate leucocyte trafficking in asthma by activating adhesion systems in the vascular endothelium.

Interleukin-5 has also been identified as a key mediator in the aetiology of asthma. Interleukin-5 not only regulates the growth, differentiation, and activation of eosinophils, but also provides an essential signal for the induction of eosinophilia during allergic inflammation. Furthermore, in conjunction with chemokines (RANTES, monocyte chemoattractant protein-3, macrophage inflammatory protein-1z and eotaxin) and lipid mediators (platelet-activating factor and leukotriene B4), IL-5 may promote eosinophil chemotaxis. Notably, of the cytokines/chemokines implicated in modulating eosinophilic inflammation, only IL-5 and eotaxin have been identified to selectively regulate eosinophil trafficking. Eotaxin is a newly identified member of the C-C branch of chemokines and is highly potent and extremely rapid in inducing pulmonary and intradermal eosinophil recruitment (recently, eotaxin-2 has been identified). Investigations in guinea-pigs and mice suggest that eotaxin and IL-5 act cooperatively to promote the recruitment of eosinophils into tissues. Evidence is also accumulating that eotaxin may play a role in the aetiology of eosinophil-associated allergic disease in humans.

Thus, the postulated role of leucocytes in the pathophysiology of asthma, in association with evidence indicating that cytokines are up-regulated in this disease, suggests that therapeutics that target these inflammatory molecules may be effective in the relief of airways obstruction.

Role of cytokines in regulating airway eosinophilia and allergic airway disease

Role of IL-5

The immunomodulatory functions of IL-4, IL-5 and eotaxin have identified these cytokines as key therapeutic targets for the relief of airway inflammation and obstruction in asthma. Interleukin-5 plays a central role in eosinophil development and activation and has been strongly implicated in the aetiology of allergic and non-allergic asthma. In transgenic mice the overexpression of IL-5 in the respiratory epithelium results in changes to the airways pathognomonic of asthma and in enhanced bronchial reactivity. Investigations in IL-5-deficient (IL-5−/−) mice indicate that this cytokine is critical for regulating eosinophilia during allergic inflammation. Moreover, in a mouse model of asthma, IL-5 was found to be essential for the development of airway epithelial cell damage and bronchial hyperreactivity in response to inhaled allergen. Expression of IL-5 by recombinant vaccinia viruses instilled into the airways of IL-5−/− mice, or delivery of recombinant protein via the peritoneal cavity, completely restored aeroallergen-induced eosinophilia and allergic disease. Notably, eosinophilia could not be restored by delivery of recombinant proteins in either compartment in the absence of allergen (see later). Recently, we have also shown that IL-5 secreted from allergen-specific CD4+ Th2 cells plays a pivotal role in the pathophysiology of allergic airway disease by regulating eosinophilia and bronchial hyperreactivity in response to allergen inhalation (and see following section). Notably, IL-5 deficiency does not affect the production of other cytokines or antibodies, nor does it significantly impair T and B cell function, suggesting that antagonism of this molecule would not significantly impair other immunological responses.

Relationship between IL-5 and eotaxin for the trafficking of eosinophils to the lung and the development of airway hyperreactivity

In conjunction with IL-5, inhibition of the function of eotaxin may markedly suppress the movement of eosinophils into tissues. Eotaxin and IL-5 may act cooperatively to regulate the homing of eosinophils to sites of allergic inflammation. Interleukin-5 mobilizes eosinophils from the bone marrow and also promotes homing to the site of inflammation, while eotaxin elicits signals for cell polarization and chemotaxis within the inflamed tissue. It appears that ‘cross talk’ occurs between IL-5 and eotaxin signalling systems to uniquely and selectively promote eosinophil chemotaxis/locomotion and potentially degranulation. Investigations using inhibitory mAbs in guinea-pigs indicated that this chemokine may play a major role in the movement of eosinophils from the blood to the allergic lung. In contrast, eosinophilia in eotaxin-deficient mice was only attenuated during the early and not the late phases of allergic airway inflammation. Recently, the eotaxin receptor has also been identified on memory Th2 cells, suggesting that eotaxin may also play a role in the recruitment of this T cell to sites of allergic inflammation. The biological functions of eotaxin suggest that this molecule, in conjunction...
with IL-5, may provide an important new therapeutic target for the attenuation of the progression of allergic disease.

While the presence of increased numbers of eosinophils in the airway mucosa is a characteristic feature of asthma, the mechanisms underlying the selective trafficking of this leucocyte to the lung are unknown. It is clear from investigations with IL-5−/− mice that the absence of IL-5 alone can abolish tissue and blood eosinophilia and the characteristic pathology and changes in airway function generated by allergic inflammation of the lung. However, it is also clear that other factors released from the site of antigen challenge are required to amplify the IL-5 signal that leads to airway eosinophilia and the features of allergic airway disease. Recently, we have defined the relationship between IL-5 and eotaxin for the recruitment of eosinophils to the airways and for the subsequent onset of bronchial hyperreactivity. Interleukin-5 and/or eotaxin were transiently expressed (over 4 days) in the airways of naive mice by the delivery of recombinant vaccinia viruses engineered to express these factors. Both cytokines induced a selective airway eosinophilia that was markedly potentiated by increasing the number of circulating eosinophils by pulsing intravenously with IL-5. Co-expression of these cytokines in the airways resulted in the synergistic amplification of the number of eosinophils recruited to the airways. The numbers of neutrophils, monocytes and lymphocytes in the BALF were not significantly increased by the expression of either cytokine. Notably, the selective airway eosinophilia induced by these cytokines did not induce airway hyperreactivity to spasmogenic stimuli. Direct inhalation of antigen, however, induced eosinophil degranulation and enhanced airway reactivity to spasmogenic stimuli. Moreover, eosinophil activation and airway hyperreactivity was directly inhibited by treatment with anti-CD4+ mAbs during allergen inhalation. Although these investigations showed a key role for these cytokines in the selective regulation of eosinophil trafficking to the lung, they also highlight the requirement of factors associated with antigen processing and CD4+ T cell activation in the mechanism of eosinophil-regulated airway hyperreactivity. It will be of interest to determine what factors elicited during the early phases of airway exposure to allergens prime eosinophils for subsequent degranulation.

**Role of IL-4**

Blocking the actions of IL-4 may also provide an effective mechanism to attenuate inflammation of the airways in asthmatics. Inhibition or deletion of IL-4 during allergic airway inflammation attenuates eosinophilia, IgE production and bronchial hyperreactivity, while overexpression of this cytokine in the lung of transgenic mice results in morphological changes to the respiratory epithelium. Recently, IL-4 was also shown to play a crucial role for the homing of Th2 cells to the lung.

Although blocking the actions of IL-4 may provide an effective mechanism for the relief of airway obstruction in asthma, evidence from animal models of Th2-dependent allergic airway inflammation indicates that targeting this cytokine alone may not be an effective therapeutic strategy. Notably, enhanced reactivity to cholinergergic stimuli and eosinophilia are still features of inflammatory responses (albeit significantly reduced) in mice treated with anti-IL-4 mAbs or that are deficient in this factor. Furthermore, unlike IL-5 transgenic mice, overexpression of IL-4 in the airway wall does not result in the induction of airway hyperreactivity, although morphological changes in the respiratory epithelium are observed. Anti-IL-4 mAbs also are only effective in attenuating aeroallergen-induced airway hyperreactivity if administered during the primary sensitization phase, but not during the period of direct provocation of the airways with allergen, suggesting that antagonists of the actions of IL-4 during an established asthmatic response may not attenuate bronchial hyperreactivity. Eosinophilia and bronchial hyperreactivity are also induced after allergen inhalation in sensitized mast cell-, IgE- and CD40- (no production of IgE, IgG or IgA) deficient mice, components of the inflammatory response whose functions are intimately regulated by IL-4. Furthermore, IL-13 has similar biological activities to IL-4 in the down-regulation of pro-inflammatory cytokines and chemokine production, in the induction and expression of integrins and in the regulation of IgE synthesis. Thus, targeting both of these cytokines (IL-4, IL-13) concurrently may be required to attenuate the asthmatic response.

Recently, IgE has been proposed to mediate IL-5 and eosinophil-dependent airway hyperreactivity and to regulate the recruitment of eosinophils to the airways in response to inhaled allergens. The precise mechanisms underlying IgE regulation of these processes is unknown. IgE-CD23 complexes on B cells have been proposed to regulate antigen-stimulated cytokine production from CD4+ Th2-type cells. Current *in vitro* investigations also suggest that allergen-specific IgE, IgG1, IgG3 (and under some conditions IgG2) and IgA (including secretory IgA), may trigger the release of preformed inflammatory mediators from eosinophils, which may induce airway damage and hyperreactivity. In response to sensitization and aeroallergen, CD40−/− mice did not produce detectable levels of OVA-specific IgE, IgG isoforms and IgA; however, eosinophilic inflammation, pathological changes to airway tissue and airway hyperreactivity were not impaired. Thus, no obligatory role was found for allergen-specific immunoglobulins in regulating eosinophilic inflammation and allergic airway disease.

In asthma, while it is clear that allergen-specific immunoglobulins are important regulatory molecules of allergic responses, our results suggest that other factors produced during the inflammatory response can also induce airway damage and hyperreactivity. Furthermore, generation of these factors is intimately associated with IL-5 signalling pathways and airway eosinophilic inflammation. Recently, inhibition of leukotriene B4 function was shown to inhibit eosinophil-derived pathology associated with a murine model of experimental allergic encephalomyelitis. Lipid mediators also activate eosinophils *in vitro*. Eosinophils may also act as antigen-processing cells and activate CD4+ T cells, after cytokine priming at the site of inflammation. Thus, lipid mediators and co-stimulatory signals derived from interactions between eosinophils and T cells may also provide an important mechanism for the induction of aeroallergen-induced airway disease.
Role of CD4+ lymphocytes in regulating allergic airway disease

CD4+ Th2-type cells

Although activated CD4+ T cells have been implicated in the pathogenesis of asthma, the direct contribution of this leucocyte to the induction of aeroallergen-induced bronchial hyperreactivity and lung damage is unknown. Investigations with inhibitory CD4-mAbs are not definitive, because the CD4 molecule is not only expressed on lymphocytes involved in helper function, but also on other inflammatory cells, such as eosinophils and monocytes, which are found in airway infiltrates after allergen provocation. Moreover, from previous investigations in which allergic airway responses were reconstituted in rats by adoptive transfer of CD4+ T cells, it remains unclear whether eosinophils and the onset of airway constriction was directly mediated by the adoptively transferred T cells or indirectly via T cell-dependent activation of other inflammatory cells. Evidence is also accumulating that CD8+ T cells may participate in the pathogenesis of aeroallergen-induced bronchial hyperreactivity. Recently, investigations in mice demonstrated a critical role for the CD8+ T cell subset in the regulation of airway hyperreactivity, IL-5 production and airway eosinophilia in response to antigen inhalation via the airways. Furthermore, while CD4+ Th2-type cells are thought to be the primary source of IL-5 and play a central role in regulating eosinophilia, IL-5 can also be secreted by activated mast cells and eosinophils. Circulating eosinophils may also be recruited to sites of allergen provocation by coordinate expression of a range of inflammatory cytokines and chemokine (such as eotaxin) that are secreted from inflammatory cells.

Thus, although there is circumstantial evidence that IL-5 and CD4+ T cells may regulate allergen-induced bronchial hyperreactivity, the direct contribution of CD4+ Th2-type cells and IL-5 production by this lymphocyte to the morphological and functional changes of the allergic lung is unknown. Recently, we have used a model of allergic airway inflammation and IL-5–/– mice to demonstrate that CD4+ Th2-type cells, through the secretion of IL-5, orchestrate the recruitment of eosinophils to the airways and the subsequent induction of allergic airway inflammation. Adoptive transfer of CD4+ Th2-type cells to aeroallergen-challenged OVA-sensitized IL-5–/– mice induced blood and airway eosinophilia, airway hyperreactivity to β-methacholine and morphological changes to the airways. In contrast, transfer of a CD4+ (negative) cell population to aeroallergen-challenged OVA-sensitized IL-5–/– mice did not promote eosinophilia or allergic airway inflammation. Notably, the CD4+ T cell-induced airway inflammation and changes in lung function did not require prior sensitization of mice with OVA, but was dependent on aeroallergen challenge. The location of CD4+ T cells during allergic inflammation in IL-5–/– mice was identified by assessing the secretion of IL-5. Interleukin-5 was detected in the lung and peribronchial lymph node (PBLN) and not in the spleen of OVA-sensitized and aerosolized CD4+ T cell-treated IL-5–/– mice. Thus, a direct association was observed between the presence of antigen-activated CD4+ Th2-type cells in the lungs of IL-5–/– mice and the induction of blood eosinophilia, the accumulation of eosinophils in the airways and the development of characteristics of allergic lung inflammation. Interestingly, in other investigations, adoptively transferred CD8+ T cells were also found to preferentially home to PBLN in response to OVA sensitization via the airways, suggesting that chemoattractant signals for the recruitment of both CD4+ and CD8+ T cell subsets may be elicited from the lung in response to a specific antigen.

Collectively, these experiments show a critical role for signals elicited from the lung, in response to the processing of inhaled antigen, for the subsequent recruitment and activation of airway CD4+ T cells and the induction of bronchial hyperreactivity and morphological changes to the airways. The data also indicate that OVA sensitization stimulates the expansion of OVA-reactive IL-5 producing CD4+ T cells and it is these cells that are essential for the induction of allergic airway inflammation in response to allergen provocation. Moreover, our results clearly demonstrate that CD4+ Th2-type cells can provide all the signals essential for the induction of allergen-induced bronchial hyperreactivity and lung damage, and support the concept that the accumulation and activation of airway eosinophils during the asthmatic response may be initiated and sustained by cytokines released from this lymphocyte.

Recently, other investigators have characterized the phenotype of airway T cell populations during OVA-induced allergic inflammation in mice. In support of our observations, the majority of infiltrating T cells were CD4+ expressing Th2 cytokines as well as surface markers which were indicative of memory T cells. Antigen-activated T cells have also been directly implicated in the induction of the expression of eotaxin and eosinophil recruitment to the lung. Eotaxin has been shown to play an important role in the accumulation of eosinophils to tissues in the early phases of inflammatory responses. Thus, antigen-activated T cells may play a pivotal role in the regulation of airway eosinophilia by inducing the expression of local eosinophil-specific chemoattractant signals, as well as by providing the critical signal for eosinophil mobilization from the bone marrow.

Regulation of IL-5 production, eosinophilia and allergic airway disease by CD4+ T cells independently of IL-4

Interestingly, evidence is accumulating that IL-5 production can be regulated by CD4+ T cells in the absence of IL-4. Interleukin-4–/– mice have significantly impaired CD4+ Th2-type cell responses and do not develop serum IgE responses to nematode infestation. However, they can produce IL-5 (albeit at lower levels) in response to nematode infestation and after sensitization and aerosolization with OVA, which may be derived from CD4+ T cells (non-classical Th2-type), Th0 cells or non-CD4+ cells. Experiments in sensitized and aeroallergen-challenged IL-4–/– mice clearly indicate that IL-5-producing CD4+ T cells can develop independently of IL-4 and secrete IL-5 when activated through the CD3-TCR complex. Moreover, this subpopulation of CD4+ T cells can provide
enough IL-5 during allergic inflammation of the lung to induce eosinophilia, bronchial hyperreactivity and morphological changes to the airways.\textsuperscript{29} Eosinophilic inflammation has also been observed in models of parasite infestation and malaria when IL-4 was absent during the initiation of the immune response.\textsuperscript{43,44} Thus, evidence is accumulating that CD4\(^+\) T cell subsets exist that do not require IL-4 for dedication to a phenotype that produces IL-5 and regulates eosinophilia. The pathway that activates aeroallergen-induced airway eosinophilic inflammation in an IL-4-independent manner may function to supplement responses by classical CD4\(^+\) Th2-type cells.

There is increasing interest in the discordant expression of IL-4 and IL-5 by T lymphocytes in various diseases and the lineages of these cells. Interestingly, intrinsic asthmatics show no correlation between disease and IgE production.\textsuperscript{1,45} Furthermore, respiratory secretions from these individuals are characterized by increased levels of IL-5 (but not necessarily IL-4) and activated CD4\(^+\) T cells.\textsuperscript{1,45} Characterization of the phenotype of CD4\(^+\) T cells producing IL-5 in IL-4\(^{-/-}\) mice and the factors involved in their selection and activation may provide important insights into the aetiology of intrinsic asthma. It will be of particular interest to determine if these CD4\(^+\) T cells can also produce IL-4 and provide help for IgE production. Investigations in IL-4 receptor-deficient mice indicate that these cells have the potential to produce IL-4.\textsuperscript{46}

Thus, two CD4\(^+\) T cell pathways exist for the immune system to regulate IL-5 production and eosinophilia in response to inhaled allergens; one dependent on IL-4 and the other independent of this factor. The central role of IL-5 in both T cell components of allergic disease further highlights the requirements for highly specific therapeutic agents that inhibit production and/or action of this cytokine.

**Regulation of airway hyperreactivity by CD4\(^+\) T cells independently of IL-4 and IL-5**

Although clinical and experimental investigations indicate that IL-4 and IL-5 are primary targets for the attenuation of asthma, studies in mice also suggest that directly targeting T cell activation may be required to alleviate the bronchial hyperreactivity associated with allergic inflammation of the airways.\textsuperscript{18,47–49} Recently, we have described a novel CD4\(^+\) T cell pathway in BALB/c mice that modulates allergen-induced airway hyperreactivity independently of the collective actions of IL-4 and IL-5.\textsuperscript{47} In this investigation by using IL-5\(^{-/-}\) and IL-4\(^{-/-}\) mice of the BALB/c strain in combination with inhibitory mAbs for these cytokines, we have identified two pathways which are critically regulated by CD4\(^+\) T cells that operate independently and in parallel in the development of allergic airway disease. Interleukin-5-regulated eosinophilia was critical for the induction of aeroallergen-induced lung damage in BALB/c mice and was shown, in part, to contribute to the development of airway hyperreactivity. However, a second T cell-regulated pathway which predominately regulates airway hyperreactivity and was not associated with pronounced morphological changes to the airways was also observed. This pathway appears to primarily operate in BALB/c mice because we have shown that inhibition of the actions of IL-5 or in combination with IL-4 abolishes the development of enhanced airway reactivity to spasmsogens in other strains.\textsuperscript{13,29} Thus, it is likely that the full contribution of the IL-5/eosinophil pathway to the mechanisms underlying airway hyperreactivity is masked in the BALB/c strain. Thus, results in IL-5\(^{-/-}\) BALB/c mice support observations that in this strain airway hyperreactivity can develop independently of IL-5 and eosinophilia.\textsuperscript{25} Data indicate that CD4\(^+\) T cells operate multiple pathways that can act independently to induce airway hyperreactivity. The coexistence of parallel pathways may account for the dissociation of airway eosinophilia from the development of airway hyperreactivity in some cases of asthma and in animal models of this disease.

Recently, the transfer of enriched naïve T cell populations from a strain of mice that displayed inherent airway hyperreactivity to methacholine to a hyporeactive strain conferred enhanced airway reactivity to this spasmogen in the absence of antigen challenge.\textsuperscript{47} Airway hyperreactivity was directly associated with CD4\(^+\) T cells and occurred in the absence of eosinophilia and pronounced inflammation and morphological changes to the airways. Although the mechanism of T cell activation in the absence of antigen was obscure, these investigations support our conclusion that factors secreted from CD4\(^+\) T cells play fundamental roles in determining the level of airway reactivity to cholinergic stimuli. Thus, while a number of molecules contribute to the mechanisms underlying the regulation of bronchial hyperreactivity in mice, only CD4\(^+\) T cells have been shown to exclusively regulate this process.\textsuperscript{48,49}

**Conclusions**

The proposed central role of airway inflammation in the induction and maintenance of asthmatic responses has identified molecules that specifically regulate the migration and activation of leucocytes as key therapeutic targets for the relief of airway obstruction. In asthma, leucocyte trafficking to the lung appears to be predominantly regulated by Th2 cytokines (or in particular IL-4 and IL-5) secreted from allergen-specific CD4\(^+\) T cells. Clinical and experimental investigations suggest that the delivery of specific antagonists of these molecules to the airways may provide a significant advance in the treatment of asthma. Glucocorticosteroids remain the current drugs of choice for the regulation of severe manifestations of asthma. These drugs may be effective, in part, because they suppress cytokine production (IL-4, IL-5 and others) by inflammatory cells and modify the participation of vascular adhesion systems in the inflammatory response. However, long-term glucocorticosteroid therapy is associated with harmful systemic effects and does not always relieve bronchial hyperreactivity. Clearly, new antagonists that target key molecules in the inflammatory cascade are required. While the chain of events leading to asthma involves a complex cascade of interacting cells and inflammatory mediators, the results clearly demonstrate that CD4\(^+\) Th2-type cells and IL-5 secreted from this cell, in association with the influx of
eosinophils to the site of inflammation, can provide the critical signals for the development of the pathophysiology of allergic airway inflammation. Furthermore, IL-5 plays an elemental role in amplifying selective airway eosinophilia induced by eotaxin. Collectively, our results identify CD4+ Th2-type cells and IL-5-regulated eosinophilia as key therapeutic targets for the relief of bronchial hyperreactivity in late-phase asthmatic responses.

References


