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Cytokines in asthma

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Asthma as a cell mediated immune response

Our understanding of the pathology of asthma has altered in the last 10 years and this has been reflected in changes in clinical management.[1 2] At the cellular level asthma was previously regarded as a classical type I hypersensitivity reaction of Gell and Coombs, with IgE triggered release of mast cell mediators leading to the intermittent bronchoconstriction which characterises the disease.[3] While such mechanisms should not be overlooked and may contribute to mortality in atopic subjects,[4] it is difficult to explain all features of the disease, in particular intrinsic or some forms of occupational asthma, on this basis. Post mortem studies of patients dying from asthma identified a significant mononuclear cell and eosinophil infiltration in the bronchial mucosa.[5 6] The application of fibreoptic bronchoscopy to the study of asthma has revealed that an inflammatory infiltrate is present in the bronchial mucosa, even in those with mild asthma and no current symptoms.[7–11] Eosinophil granule cationic proteins such as major basic protein (MBP) and eosinophil cationic protein (ECP) will lead to damage to bronchial epithelium in vitro at concentrations detected in vivo.[8 12–14] It is suggested that these products may contribute to the observed epithelial damage in the airways in asthma, and that these changes (in addition to the actions of eosinophil lipid mediators such as platelet activating factor and leukotriene C4) may contribute to the bronchial hyperresponsiveness to non-specific inhaled stimuli that is now included in the definition of asthma.[2 13 15] Eosinophil infiltration and activation in biopsy samples of bronchial mucosa and bronchoalveolar lavage fluid is also detected in intrinsic and occupational asthma.[16–19] Recent evidence is thus of a cellular immune response with eosinophil activation as a final common pathway in atopic and non-atopic forms of asthma. This may determine the bronchial hyperresponsiveness which predisposes to bronchoconstriction in these different manifestations of the disease, with an additional and possibly separate contribution from IgE dependent mechanisms in those with atopic asthma.

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Cytokines

Lymphokines were originally defined as cell free soluble factors generated by sensitised lymphocytes in response to specific antigen.[20] The terms cytokine and interleukin broaden the definition to factors originating from many different cell types.[21 22] Cytokines were defined initially on the basis of their actions, but the cloning of the genes for these products greatly enhanced classification and cytokine expression in vivo can now be studied at the gene, messenger RNA, or protein level.[22] Identification of cytokine genes has also allowed examination of factors regulating production of different cytokines.[23] It is the aim of this review to examine the role of different cytokines in determining the nature of the airway inflammatory response in asthma, and to outline briefly the in vitro, animal, and human studies suggesting which cytokines may be important. Rather than cataloguing the vast array of cytokines present, this article will focus on the importance of particular cytokines and how this adds to our knowledge of the actions of currently available therapeutic agents such as corticosteroids, and on cytokine targets for future more specific asthma treatment.

CYTOKINES RELEVANT TO ASTHMA

The actions of cytokines relevant to asthma are summarised in table 1.

Interleukin 5 (IL-5), together with interleukin 3 (IL-3) and granulocyte macrophage colony stimulating factor (GM-CSF), enhances human eosinophil differentiation,[24] maturation,[25 26] endothelial adherence,[27] activation,[28] and degranulation in vitro.[29] Interleukin 5 primes eosinophils for in vitro chemotaxis,[30] and in vitro data also suggest a role for IL-3 and GM-CSF in eosinophil accumulation.[31–33] Other cytokines such as IL-2,[34] IL-8,[35] and RANTES[36] have recently been shown to be eosinophil chemoattractants.

A complex array of cytokines is implicated in control of IgE synthesis by B cells.[37] In summary IgE synthesis is dependent on IL-4,[38] and is enhanced by IL-5[39] and IL-6,[40*] whereas interferon γ (IFNγ),[38] IL-8,[41] and IL-12[42] are inhibitory. These cytokines act in concert with an array of cell surface signals to activate or repress differential gene splicing which results in the productive IgE mRNA transcript.[37]

*The recently cloned T cell derived cytokine IL-13 may also have a role in IgE production.[148]

Table 1 Cytokines relevant to airway inflammation in asthma

Cytokine	*Cell source*	*Actions*
Prime suspects:		
Interleukin 5 (IL-5)	T cells Mast cells Eosinophils	Eosinophil differentiation and maturation activation endothelial adhesion priming for chemoattractants Basophil differentiation priming Cofactor for IgE synthesis
Interleukin 3 (IL-3)	T cells Mast cells Eosinophils	Granulocyte (eosinophil and neutrophil) differentiation activation in vitro survival priming chemotaxis (eosinophils)
Granulocyte macrophage colony stimulating factor (GM-CSF)	T cells Mast cells Macrophages Epithelial cells Eosinophils	Granulocyte (eosinophil and neutrophil) differentiation activation in vitro survival chemotaxis (eosinophils)
Interleukin 4 (IL-4)	T cells Mast cells	Essential for IgE synthesis T cell growth factor Increased endothelial adhesion molecule expression (VCAM-1)
Interferon γ (IFN)	T cells	Inhibition IgE isotype switch Inhibition of Th2 cell growth Eosinophil activation (late acting) Macrophage activation
Possible accomplices:		
Interleukin 1 (IL-1α and β) Tumour necrosis factor (TNF α) Interleukin 6 (IL-6)	Many cell types	Increased endothelial adhesion molecule expression T cell activation costimuli Macrophage activators Eosinophil activators
Interleukin 2 (IL-2)	T cells	T cell growth factor Eosinophil chemoattractant
Interleukin-8 (IL-8)	Monocytes T cells Fibroblasts	Neutrophil and T cell chemoattractant Neutrophil activator Inhibition of IgE synthesis Primes for eosinophil chemotaxis
Macrophage inflammatory protein-1 (MIP-1)		Monocyte and naive T cell chemoattractant Activates basophils and mast cells
RANTES	T cells Platelets	Memory T cell and eosinophil chemoattractant
Interleukin 10 (IL-10)	T cells Monocytes	Inhibition of Th1 cytokine production (action on APC) Mast cell growth (mouse)
Interleukin 12 (IL-12)	T cells	NK cell, T cell growth Inhibits IgE synthesis
Platelet derived growth factor (PDGF-β)	Monocytes Macrophages	Fibrosis Th2 cytokine inhibition
Transforming growth factor β (TGF-β)	Monocytes Macrophages	Fibrosis Th2 cytokine inhibition

Other cytokines are implicated in the inflammatory process in asthma, although their roles are less well defined. The proinflammatory cytokines tumour necrosis factor (TNF) α and IL-1 (α and β) have multiple actions including upregulation of adhesion molecules on endothelium (enhancing accumulation of leucocytes from the circulation at the site of inflammation[43 44]), monocyte activation,[45 46] increased eosinophil cytotoxicity,[47] and costimulation of T cell activation (IL-1: particularly T helper (Th2 cells).[48 49] Interleukin 2 is the major T cell growth factor,[50] although IL-1,[49] IL-4,[51] IL-7,[52] and IL-12[53] are also potentially active in T cell activation and expansion. The cytokine RANTES appears to have specific chemoattractant activity for memory T cells (that respond to recall antigens[54]), and other members of this intercrine family such as IL-8[55] and macrophage inflammatory protein 1 (MIP-1)[56] may have a role in recruitment of

lymphocytes and monocytes. Although IL-3 and IL-4 are mast cell growth factors in rodents, they do not appear to be active in human mast cell proliferation and the role of stem cell factor (SCF) in human mast cell activity in asthma remains to be defined.[57] The role of neutrophils in asthma is uncertain: although these cells are present after experimental allergen challenge and neutrophil chemoattractants distinct from IL-8 have been isolated,[58-60] increased numbers are not seen in bronchial biopsy specimens or bronchoalveolar lavage fluid from patients with non-acute asthma.[8 11] Deposition of collagen below the bronchial basement membrane is described in asthma[61] although the significance is unknown. Profibrogenic cytokines such as transforming growth factor β (TGF-β) or platelet derived growth factor β (PDGF-β) may be implicated,[62] and both of these cytokines may influence T cell responses (see below).[63 64]

Although a bewildering array of different cytokines may be involved in asthma, the important specific cytokines thus appear to be IL-5 (with IL-3 and GM-CSF) in eosinophil activation, and IL-4 in IgE regulation in atopic disease. Clearly other cytokines are implicated and, while targeting single mediators may be of value, an understanding of the cell(s) of origin and control of cytokine synthesis in asthma will be essential to future therapeutic intervention.

Patterns of T cell cytokine response which may determine immunopathology

Interaction of a specific T cell receptor with an antigen peptide complexed with major histocompatibility products on antigen presenting cells is the principal initiating event in specific immune responses leading to immunoglobulin synthesis or cellular activation.[65 66] In vitro and animal studies have defined the pivotal role of T lymphocyte and T cell derived cytokines in the control of eosinophil differentiation and activation and IgE synthesis.[37 38 67 68] There is now considerable evidence for activation of Th lymphocytes (CD4+) in asthma (table 2).

Table 2 Evidence for CD4+ T cell activation in asthma

Increased peripheral blood CD4+ activation markers in acute severe asthma
Increased expression of CD25 (IL-2 receptor) in bronchial biopsies from atopic, intrinsic and occupational asthmatics compared with biopsies from control subjects by immunohistology
Increased CD25 expression by CD4+ T cells in bronchoalveolar lavage fluid from atopic and intrinsic asthmatics. Correlation with bronchoalveolar lavage fluid eosinophils, airflow obstruction and bronchial responsiveness
Changes in CD4+ T cells in blood and bronchoalveolar lavage fluid after allergen challenge of atopic asthmatics
Depletion of CD4+ cells inhibited eosinophil accumulation and hyperresponsiveness in an animal challenge model

Examination of cytokines produced by mouse Th clones grown in vitro showed that different clones produced different patterns of cytokines.[69] These different patterns were predicted to have differing functional effects, and the concept arose that the profile of cytokines produced by Th cells might determine the nature of the ensuing inflammatory response.[70 71] At one extreme the Th1 pattern of cytokine production was characterised by IL-2 and IFNγ, but little or no IL-4 and IL-5, while the Th2 clones produced IL-4 and IL-5, but little or no IL-2 or IFNγ. Both types of Th clones produced IL-3 and GM-CSF. The functional significance of this observation was shown by the demonstration that Th1 clones were poor at helping antibody synthesis in vitro leading to IgG_{2a}, whilst Th2 products enhanced immunoglobulin synthesis leading to IgG_1 and IgE.[72] Transfer of Th1 clones to donor mice produced delayed type hypersensitivity reactions which were not seen with Th2 clones,[73] and this could be blocked by antibodies to IFNγ.[74] Th1-like cell lines were isolated from animals infected with *Brucella abortus* which produces a delayed type hypersensitivity response, whilst Th2 lines predominated in animals parasitised with *Nippostrongylus brasiliensis* which produces a pronounced eosinophilia and IgE response.[75] The response of mice infected with *Leishmania major* could be manipulated by antibodies to different cytokines, indicating the importance of the cytokine response in determining pathology.[76] Development of either a Th1 or Th2 pattern of cytokine synthesis by both murine and human T cells expanded in vitro is enhanced by IFNγ or IL-4 in the culture medium respectively,[77-79] and TGF-β and PDGF-β inhibit Th2 cytokine production in the murine system.[63 64] The local cytokine microenvironment may thus contribute to the nature of the T cell response, which in turn may determine the type of cellular response which follows.[80]

If different T cell cytokine responses determine the inflammatory response in animals, what evidence is there of differing responses in human disease, and particularly in asthma? Initial analysis of human T cell clones failed to show a Th1/Th2 pattern[81] but it is now clear that certain antigens can direct a Th1 or Th2 response.[82] In particular, allergen specific T cell clones produce a preponderance of IL-4 and IL-5, but little IL-2 or IFNγ, and might be expected to participate in IgE and eosinophil responses in allergic disease.[82 83] Such Th2-like clones have been derived from the conjunctiva of subjects with vernal conjunctivitis[84] and the skin of subjects with atopic dermatitis.[85] By in situ hybridisation cells expressing mRNA for IL-3, IL-4, IL-5 and GM-CSF, but not IL-2 or IFNγ, were detected after cutaneous and nasal allergen provocation,[86 87] whereas IL-2 and IFNγ mRNA positive cells were predominant in the cutaneous tuberculin response.[88] More recently IL-2 and IFNγ mRNA were detected in tuberculoid leprosy skin lesions by polymerase chain reaction (delayed type hyper-

sensitivity response) whereas IL-4 and IL-5 were present in lepromatous lesions, supporting the concept that production of differing patterns of cytokines might lead to different immunopathological responses in vivo.[89]

Evidence for involvement of cytokines in asthma

STABLE MILD ASTHMA

Sera and peripheral blood T cell culture supernatants from subjects with asthma were shown to support eosinophil survival in vitro.[90] The serum activity was inhibited by antibodies to IL-5 and GM-CSF but not to IL-3, whereas the T cell supernatant activity appeared to be principally GM-CSF and was derived from the CD4+ subset (with no activity from CD8+ T cells). Detection of cytokine protein in bronchoalveolar lavage fluid is hampered by the sensitivity of currently available assays, and the problems of variable dilution of the epithelial lining fluid by instilled saline. However, IL-4 and IL-5 were detected in 18–21 fold concentrated bronchoalveolar lavage fluid from subjects with atopic asthma by immunoenzymatic and bioassay respectively, whereas IL-2 and IFNγ were present in much lower concentrations.[19] In situ hybridisation studies of cells from bronchoalveolar lavage fluid from atopic asthmatic patients demonstrated increased proportions of cells in the bronchoalveolar lavage fluid with signals for IL-2, IL-3, IL-4, IL-5, and GM-CSF mRNA when compared with non-smoking non-atopic control subjects, but no difference in numbers of cells in bronchoalveolar lavage fluid expressing IFNγ mRNA.[91] In a separate study the numbers of cells in bronchoalveolar lavage fluid expressing TNFα mRNA were shown to be increased in stable atopic asthmatic patients compared with controls.[92] Interleukin-5 mRNA was detected in bronchial biopsy samples from symptomatic mild asthmatic patients, but not from asymptomatic asthmatic patients or non-atopic controls.[93] Correlations were reported between IL-5 mRNA expressing cells in bronchial biopsy samples and numbers of CD25 positive cells (putative activated T cells) and activated eosinophils.[93] Relationships were also reported between IL-5 activity in concentrated bronchoalveolar lavage fluid and eosinophil numbers in bronchoalveolar lavage fluid and CD4+ T cell activation,[19] supporting a link between IL-5 and eosinophils in asthma in vivo. Comparison of the proportions of cells in bronchoalveolar lavage fluid with positive in situ hybridisation signals from subjects with current asthma symptoms (median forced expiratory volume in one second (FEV_1) 82% predicted, and methacholine PC_{20} 0·6 mg/ml) and asymptomatic seasonal asthmatic subjects (median FEV_1 103%, PC_{20} 10·4 mg/ml) showed increased expression of mRNA for IL-3, IL-4, IL-5, and GM-CSF in those with symptoms, but no differences between the groups in cells expressing IL-2 or IFNγ mRNA.[94] Furthermore, relationships were observed between proportions of IL-4 and IL-5 mRNA positive cells in bronchoalveolar lavage fluid and both airway obstruction and bronchial responsiveness. Broide and coworkers detected increased concentrations of TNFα, GM-CSF, and IL-6 in bronchoalveolar lavage fluid from symptomatic asthmatic subjects (mean FEV_1 59% predicted) when compared with asymptomatic subjects (FEV_1 86%), whereas IL-2 and IL-1β were detected in equal quantities in both groups.[95] Interleukin-1α and IL-4 were not detected in bronchoalveolar lavage fluid from asthmatic subjects in this study although, unlike the previously described reports, the study group included patients receiving a wide range of medications and corticosteroids were given to those with symptoms before the study.

There is little information on cytokines in intrinsic asthma. Concentrated bronchoalveolar lavage fluid from intrinsic asthmatic subjects showed detectable quantities of IL-2 and IL-5 but, in contrast to atopic subjects in the same study, IL-4 was not detected.[19]

ACUTE SEVERE ASTHMA

Sera from subjects admitted to hospital with acute severe asthma had detectable concentrations of IFNγ which correlated with FEV_1 and decreased as patients responded to corticosteroid therapy.[96] In a separate study patients with exacerbations of their disease requiring outpatient treatment with oral prednisolone had serum IL-5 concentrations detectable by immunoenzymatic assay.[97] Clearly, in acute severe asthma the immunopathology may differ from chronic airway disease, and the detected cytokines may reflect a response to the initiating event (such as viral infection), in addition to reflecting changes associated with ongoing asthma.

Allergen challenge studies

The allergen induced late asthmatic response provides an experimental model for atopic allergic asthma.[98] Fibreoptic bronchoscopy performed at various times after challenge demonstrates eosinophil accumulation and activation,[99] together with changes in T cells.[100 101] Broide and coworkers detected GM-CSF in bronchoalveolar lavage fluid obtained 24 hours after allergen challenge, and by in situ hybridisation showed that mRNA was predominantly localised to lymphocytes within the fluid.[102] We have recently completed a randomised study comparing cells in bronchoalveolar lavage fluid obtained 24 hours after allergen or diluent control challenge in mild atopic asthmatic subjects. There was a significant increase in the number of eosinophils and CD4+ T cell activation after allergen challenge, and this was accompanied by increased numbers of cells in the fluid positive for IL-4, IL-5, and GM-CSF mRNA. There was no difference in numbers of cells in the bronchoalveolar lavage fluid expressing IL-2, IL-3, or IFNγ

mRNA when allergen and diluent control challenge were compared.[103] Interleukin-5 was detected by immunoenzymatic assay in bronchoalveolar lavage fluid obtained 48 hours after local instillation of allergen into the airways of non-asthmatic atopic subjects and this was associated with an increase in the number of eosinophils.[104]

Effects of corticosteroids on cytokines in asthma

Corticosteroid therapy reduces symptoms and bronchial responsiveness and improves lung function in asthma.[105] Corticosteroids are now widely used as anti-inflammatory treatment in asthma, in accordance with current guidelines.[106 107] In vitro studies suggest that corticosteroids act to inhibit cytokine production.[108-110] Is there evidence for such a role in vivo in asthma? Inhaled corticosteroids reduced eosinophil infiltration and activation in bronchoalveolar lavage fluid and bronchial biopsy samples in asthma, and T cell numbers in bronchial biopsy samples were reduced.[111-113] Oral prednisolone treatment was associated with a reduction in serum IFNγ in acute severe asthma, and serum IL-5 fell to undetectable concentrations after one week of prednisolone treatment in subjects with exacerbations of their disease.[97] We have recently studied the effects of two weeks of oral prednisolone treatment on eosinophils, T cell activation and cytokine mRNA expression in bronchoalveolar lavage fluid in a double blind placebo controlled study in symptomatic asthma. When subjects receiving prednisolone were compared with those treated with placebo, a significant fall in bronchial responsiveness was associated with a fall in eosinophils in the bronchoalveolar lavage fluid. Furthermore, this was associated with a significant reduction in the proportion of cells in the fluid expressing mRNA for IL-4 and IL-5, whereas there was an increase in IFNγ mRNA positive cells.[114] Thus corticosteroid therapy in asthma was associated with modulation of cytokine gene expression. Cyclosporin A is a potent inhibitor of T cell IL-2 gene expression in vitro, with well defined specific molecular targets.[115] This agent produced a significant improvement in steroid dependent asthmatic subjects, possibly reflecting actions on cytokine gene expression.[116]

Table 3 Evidence for IL-5 as a determinant of eosinophil activation in asthma

IL-5 activity detected in serum and bronchoalveolar lavage fluid from atopic and intrinsic asthmatics
IL-5 mRNA positive cells increased in bronchoalveolar lavage fluid and bronchial biopsies from asthmatics compared with control subjects
Increased IL-5 protein and mRNA after allergen challenge
Decreased IL-5 protein and mRNA after corticosteroids
Recombinant IL-5 applied topically to the upper airway mucosa associated with eosinophils and increased histamine responsiveness
Anti-IL-5 monoclonals block eosinophilia in animal challenge models

Cell source of cytokines in asthma: Th2 cells in vivo?

Current evidence supports a role for IL-5 in the initiation and maintenance of eosinophilic bronchial inflammation in asthma, and suggests that successful treatment is associated with inhibition of IL-5 production. Evidence from animal experiments also supports a pivotal role for IL-5 in asthma (table 3). Interleukin-4, unopposed by IFNγ, may be important in atopic asthma.

An important question remains. Which cell types are responsible for production of cytokines in the airway in asthma? Although IL-4 and IL-5 were initially described as T cell products, other cell types may produce these and other cytokines. Murine mast cell lines can produce IL-3, IL-4, IL-5, TNFα, and GM-CSF,[117-119] and human cells of mast/basophil lineage are also capable of cytokine synthesis.[120] Alveolar macrophages from asthmatic subjects spontaneously produce GM-CSF in vitro.[121] More recently in vitro production of several cytokines by eosinophils (IL-3,[122] IL-5,[123] IL-6,[124] IL-8,[125] GM-CSF[126]), and bronchial epithelial cells (GM-CSF, IL-8) has been reported.[127] Messenger RNA for GM-CSF and IL-5 was localised to eosinophils, in addition to mononuclear cells, in bronchoalveolar lavage fluid obtained after local allergen challenge of atopic asthmatic subjects.[128] It is now clear that many cell types may contribute cytokines which act in either an autocrine or paracrine manner. Whether this occurs in vivo in asthma is not yet clear.

Immunomagnetic separation of cells in bronchoalveolar lavage fluid before in situ hybridisation studies and combined immunocytochemistry and in situ hybridisation have shown that most cytokine mRNA for IL-4 and IL-5 in atopic asthmatic subjects originates from T lymphocytes.[91] Both IL-4 and IL-5 were also localised to bronchoalveolar lavage T cells obtained 24 hours after allergen challenge.[104] However, initial reports of combined immunocytochemistry for cytokine protein and cell surface markers suggest that the majority of detectable IL-4 in bronchial biopsy specimens is associated with mast cells.[129] How can these findings be reconciled? It is possible that mast cells store cytokines[118] and thus have detectable quantities for immunocytochemical studies, whereas T cells secrete in a polarised fashion[130] and cytokine product may be fleeting and thus difficult to detect. Both cell types are likely to contribute to airway inflammation in asthma. Mast cell IL-4 may prime T cell activation to a predominant IL-4/IL-5 pattern, since in both murine and human T cell cloning IL-4

Table 4 Therapeutic modulation of cytokines: potential approaches

Anticytokine monoclonal antibodies
Cytokine receptor antagonists
Novel agents acting on gene regulation
Altered response to T cell activation (specific immunotherapy)
Opposing cytokines

favours development of Th2-like clones.[78 79] Murine Th1 and Th2 clones are reported to differ in a number of important respects in activation and signalling[131 132] and, if different subtypes of human Th cells do indeed exist, such differences could provide a target for selective therapeutic manipulation.

Potential value of novel cytokine directed therapy

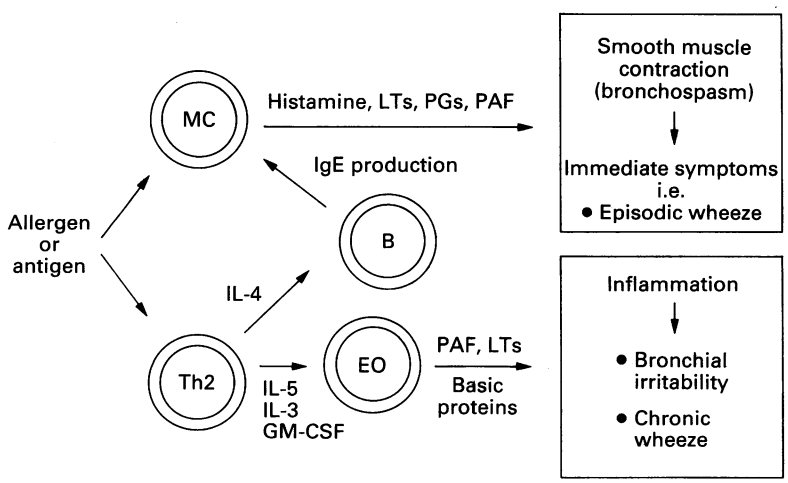
The therapeutic options for altering cytokine gene expression in asthma are summarised in table 4. Anticytokine antibodies have been shown to alter the pathology resulting from *Leishmania major* infection in different strains of laboratory mice. Strains that usually mount a non-healing fatal Th2 type T cell response can be converted to a healing outcome by the administration of anti-IL-4 monoclonal antibodies.[133] Anti-IL-5 inhibited the eosinophilic response to helminthic infection in mice,[134] and also inhibited lung eosinophil infiltration in experimental animal antigen challenge models of asthma.[135] Whether such approaches would be useful in a chronic human disease is unlikely; one could not treat before initiation of disease, and immune responsiveness is likely to develop to foreign antibodies.

As the genes for many cytokine receptors (including IL-5[136]) are cloned, it should become possible to develop specific anticytokine receptor antagonists. Anti-IL-1R and anti-IL-4R have been shown to delay allograft rejection in experimental animals,[137 138] and IL-5R might allow specific intervention in asthma.[139] Such an approach would reveal the true importance of eosinophils to asthma, but might also reveal the as yet unknown role of IL-5 in other immune functions.

As the molecular basis of gene activation is clarified at the level of regulatory proteins acting on gene promoter elements, this might allow intervention in gene activation or repression. Further elucidation of the actions of corticosteroids and agents such as cyclosporin A at this molecular level may allow design of novel compounds. As yet little is known about IL-5 gene regulation, although the genes for IL-3, IL-4, IL-5, and GM-CSF are all clustered on the long arm of human chromosome 5[140] and there may be common transactivating factors

There is both in vitro and in vivo evidence that induction of T cell anergy[141] and immunotherapy[142] may modify the T cell cytokine response to allergens. Development of specific peptides or agents interfering with T cell costimulatory signals may allow more specific therapeutic intervention.[143]

A number of cytokines oppose the actions of other cytokines. Interleukin-10 (cytokine synthesis inhibitory factor) inhibits the production of Th1 cytokines in vitro[144 145] and IFNγ inhibits Th2 proliferation.[78] Interferon γ enhanced clinical response to treatment in leishmaniasis,[146] possibly by altering cytokine responses. However, both cytokines have multiple actions and a trial of IFNγ in allergic rhinitis produced no significant clinical effects or suppression of IgE concentrations.[147]



Hypothesis of cellular and cytokine interaction in pathogenesis of atopic asthma. MC—mast cell; IL—interleukin; GM-CSF—granulocyte macrophage colony stimulating factor; Th2—Th2 type CD4 + T lymphocyte; B—B lymphocyte; EO—eosinophil; LT—leukotriene; PGs—prostaglandins; PAF—platelet activating factor.

Conclusion

A number of important cytokines contributing to airway inflammation in asthma have been described and a hypothesis of interactions of cell and cytokines in the airway in asthma, based on available evidence, is shown (fig). In particular, IL-5 may be important in the control of eosinophil mediated airway changes. Although it is likely that an increasingly complex network of cytokines involved in asthma will be described, further understanding of the mechanisms regulating these processes at the cellular and molecular level should allow the development of novel therapeutic strategies.

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