Occasional review

Cytokines in asthma

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Cytokines are usually extracellular signalling proteins, usually less than 80 kD in size, and many are glycosylated. They are produced by many different cell types that are involved in cell-to-cell interactions acting through specific receptors on the surface of target cells. Cytokines usually have an effect on closely adjacent cells and therefore function in a predominantly paracrine fashion, although they may also act at a distance (endocrine) and may have effects on the cell of origin (autocrine). Cytokines may be regarded as a mechanism for cell-cell communication, and within this group may be included growth factors and cytokines with primarily chemoattractant properties (chemokines). They act on target cells to cause a wide array of cellular functions including activation, proliferation, chemotaxis, immunomodulation, release of other cytokines or mediators, growth and cell differentiation, and apoptosis. Cytokines were originally characterised (and named) according to some aspect of their functional activity that was initially discovered, but the cloning of the genes for these cytokines has now provided a better insight into their classification and grouping. It is apparent that there is a wide pleiotropy and element of redundancy in the cytokine family in that each cytokine has many overlapping functions, with each function potentially mediated by more than one cytokine.

The effect of an individual cytokine in the context of disease may not be easy to predict because it may be influenced by other cytokines released simultaneously from the same cell or from target cells following activation by the cytokine. The effects of cytokines are mediated by binding to cell surface high affinity receptors usually present in low numbers. The number of these receptors can be upregulated with cell activation, and there the effect of a cytokine may depend on the modulation of its receptors. Cytokines themselves may induce the expression of receptors which may change the responsiveness of both source and target cells. Two examples are the actions of interferon γ (IFN-γ) in decreasing the effect of tumour necrosis factor α (TNF-α) receptors on macrophages[1] and that of interleukin 1β (IL-1β) in increasing the expression of the same receptors.[2] Some cytokines may stimulate their own production in an autocrine manner, whereas others stimulate the synthesis of different cytokines that have a feedback stimulatory effect on the first cytokine resulting in an increase in its effects.

Inflammation in asthma

Cytokines play an integral role in the coordination and persistence of the inflammatory process in the chronic inflammation of the airways in asthma since they are capable of inducing many of the pro-inflammatory effects characteristic of this disease (table 1). Many cytokines are expressed and their function in this process can be surmised from a knowledge of their properties or from information obtained from animal studies. The chronic airway inflammation of asthma is unique in that the airway wall is infiltrated by T lymphocytes, eosinophils, macrophages/monocytes and mast cells, and sometimes by neutrophils too.[3–6] In addition, an acute-on-chronic inflammation may be observed with acute exacerbations, with an increase in eosinophils and neutrophils in the airway submucosa and release of mediators such as histamine and cysteinyl leukotrienes (cys-LTs) from eosinophils and mast cells to induce bronchoconstriction, airway oedema, and mucus secretion. Changes in the resident cells are also observed in the asthmatic airway—for example, an increase in the thickness of the airway smooth muscle with hypertrophy and hyperplasia,[7] more myofibroblasts with an increase in collagen deposition in the lamina reticularis,[8] more vessels[9] and an increase in the goblet cell numbers in the airway epithelium.[10] Clearly, these chronic and acute inflammatory changes observed in the asthmatic airway could result from excessive release of many types of cytokines which has been observed in experimental induction of asthma by allergen exposure and virus infections, or during symptomatic asthma.[11–14] Not only are cytokines involved in maintaining the chronic inflammatory process, they are also responsible for the initiation or the early stages of this process.

It is not simple to classify the numerous cytokines that are potentially involved in asthma because of their pleiotropic nature and overlapping properties. However, with regard to the specific abnormalities of asthma and to our current understanding of the pathogenesis of asthma, they may be grouped as follows:

(1) Lymphokines: IL-2, IL-3, IL-4, IL-5, IL-13, IL-15, IL-16, IL-17.
(2) Pro-inflammatory cytokines: IL-1, TNF, IL-6, IL-11, GM-CSF, SCF.

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Table 1   Summary of effects of cytokines

	Important cellular and mediator effects
Lymphokines	
IL-2	• Eosinophilia in vivo
	• Growth and differentiation of T cells
IL-3	• Eosinophilia in vivo
	• Pluripotential haematopoietic factor
IL-4	• Eosinophil growth ↑
	• Th2 cells ↑; Th1 cells ↓
	• IgE ↑
IL-5	• Eosinophil maturation
	• Apoptosis ↓
	• Th2 cells ↑
	• BHR
IL-13	• Activates eosinophils
	• Apoptosis ↓
	• IgE ↑
IL-15	• As for IL-2
	• Growth and differentiation of T cells
IL-16	• Eosinophil migration
	• Growth factor and chemotaxis of T cells (CD4+)
IL-17	• T cell proliferation
	• Activates epithelia, endothelial cells, fibroblasts
Pro-inflammatory	
IL-1	• Adhesion to vascular endothelium ↑; eosinophil accumulation in vivo
	• Growth factor for Th2 cells
	• B cell growth factor; neutrophil chemoattractant; T cell and epithelial activation
	• BHR
TNF-α	• Activates epithelium, endothelium, antigen presenting cells, monocytes/macrophages
	• BHR
IL-6	• T cell growth factor
	• B cell growth factor
	• IgE ↑
IL-11	• B cell growth factor
	• Activates fibroblast
	• BHR
GM-CSF	• Eosinophil apoptosis and activation; induces release of leukotrienes
	• Proliferation and maturation of haematopoietic cells; endothelial cell migration
	• BHR
SCF	• VCAM-1 on eosinophils ↑
	• Growth factor for mast cells
Inhibitory cytokines	
IL-10	• Eosinophil survival ↓
	• Th1 and Th2 cells ↓
	• Monocyte/macrophage activation ↓; B cells ↑; mast cell growth ↑
	• BHR ↓
IL-1ra	• Th2 proliferation ↓
	• BHR ↓
IFN-γ	• Eosinophil influx after allergen ↓
	• Th2 cells ↓
	• Activates endothelial cells, epithelial cells, alveolar macrophages/monocytes
	• IgE ↓
	• BHR ↓
IL-18	• via IFN-γ release ↓
	• Releases IFN-γ from Th1 cells
	• Activates NK cells, monocytes
	• IgE ↓
Growth factors	
PDGF	• Fibroblast and airway smooth muscle proliferation
	• Release of collagen
TGF-β	• T cell proliferation ↓
	• Blocks IL-2 effects
	• Fibroblast proliferation
	• Chemoattractant for monocytes, fibroblasts, mast cells
	• ASM proliferation ↓

IL = interleukin; TNF = tumour necrosis factor; GM-CSF = granulocyte-macrophage colony stimulating factor; SCF = stem cell factor; IFN = interferon; PDGF = platelet derived growth factor; NK = natural killer; Th cells = T helper cells; BHR = bronchial hyperresponsiveness; VCAM = vascular adhesion molecule; ASM = airway smooth muscle.

Figure 1   Scheme of cytokines involved in antigen presentation, activation of T helper progenitor (Thp) cells preferentially into Th2 rather than Th1 cells, and the effects of these cytokines. For abbreviations, see text.

phocytes are of the T helper type 2 (Th2).[15–17] The primary signals that activate Th2 cells are unknown but may be related to the presentation of a restricted panel of antigen in the presence of appropriate cytokines. Dendritic cells are ideally suited to being the primary contact between the immune system and external allergens. Co-stimulatory molecules on the surface of antigen presenting cells, in particular B7.2/CD28 interaction, may lead to proliferation of Th2 cells (fig 1).[18] With the expression of IL-4, synthesis of IgE by B lymphocytes on immunoglobulin isotype switching occurs.[19] Other cytokines, including TNF-α and IL-6 may also be important. The IgE produced in asthmatic airways binds to FcεRI receptors ("high affinity" IgE receptors) on mast cells, priming them for activation by antigen. The development of mast cells from bone marrow cells represents a process of maturation and expansion involving growth factors and cytokines such as stem cell factor (SCF) and IL-3 derived from structural cells. Mast cells recovered by bronchoalveolar lavage from asthmatic subjects show an enhanced release of mediators such as histamine.[20] Mast cells also elaborate IL-4 and IL-5.[21]

IL-4 also increases the expression of an inducible form of the low affinity receptor for IgE (FcεRII or CD23) on B lymphocytes and macrophages.[22] This may also account for the increased expression of CD23 on alveolar macrophages from asthmatic patients,[23] which in turn could account for the increased release of cytokines from these macrophages.[24 25] In addition, IL-4 is very important in driving the differentiation of CD4+ Th precursors into Th2-like cells.

The differentiation, migration and pathobiological effects of eosinophils may occur through the effects of GM-CSF, IL-3, IL-5 and certain chemokines such as eotaxin.[26–31] IL-5 and eotaxin also induce the mobilisation of eosinophils and eosinophil precursors into the circulation.[32 33] Once recruited from the circulation, mature eosinophils in the presence of these cytokines change phenotype into hypodense eosinophils which show increased sur-

(3) Anti-inflammatory cytokines: IL-10, IL-1ra, IFN-γ, IL-12, IL-18.

(4) Chemotactic cytokines (chemokines): RANTES, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIP-1α, eotaxin, IL-8.

(5) Growth factors: PDGF, TGF-β, FGF, EGF, IGF.

Role and source of cytokines in asthma

The CD4+ T lymphocytes of the asthmatic airways express a panel of cytokines including IL-3, IL-4, IL-5, IL-10, IL-13 and granulocyte-macrophage colony stimulating factor (GM-CSF), indicating that these T lym-
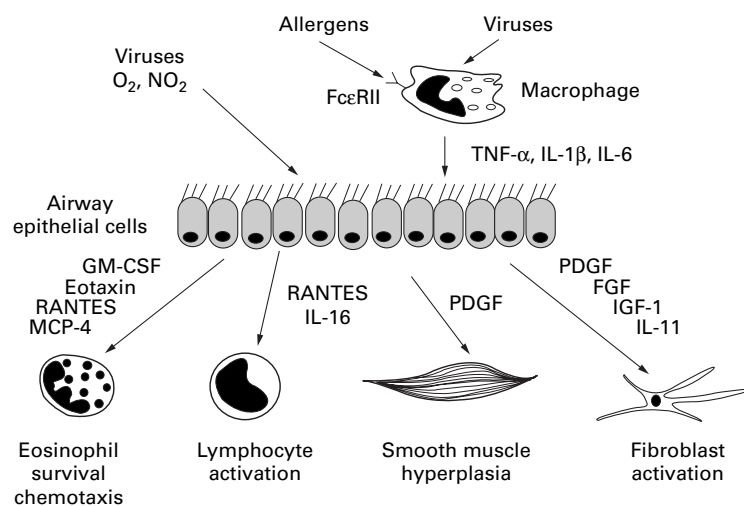
Figure 2 Cytokines released from airway epithelial cells following various stimuli and other cytokines released from other cells such as macrophages. Cytokines from airway epithelial cells have effects on other cell types such as eosinophils, lymphocytes, airway smooth muscle cells, and fibroblasts. For abbreviations, see text.

vival in bronchial tissue.[34][35] These eosinophils are primed for ligand mediated generation of increased amounts of cys-LTs and for cytotoxicity to other cells such as the airway epithelium.[36–38] Eosinophils themselves may also generate other cytokines such as IL-3, IL-5, and GM-CSF.[39][40]

Cytokines may also play an important role in antigen presentation (fig 1) and may enhance or suppress the ability of macrophages to act as antigen presenting cells. Normally, airway macrophages are poor at antigen presentation and suppress T cell proliferative responses (possibly via release of cytokines such as IL-1 receptor antagonist), but in asthma there is evidence for reduced suppression after exposure to allergen.[41][42] Both GM-CSF and IFN-γ increase the ability of macrophages to present allergen and express HLA-DR.[43] IL-1 is important in activating T lymphocytes and is an important co-stimulator of the expansion of Th2 cells after antigen presentation.[44] Airway macrophages may be an important source of "first wave" cytokines such as IL-1, TNF-α and IL-6, which may be released on exposure to inhaled allergens via FcϵRII receptors. These cytokines may then act on epithelial cells to release a second wave of cytokines, including

GM-CSF, IL-8, and RANTES, which then amplify the inflammatory response and lead to influx of secondary cells such as eosinophils, which themselves may release multiple cytokines (fig 2).

Cytokines may also exert an important regulatory effect on the expression of adhesion molecules, both on endothelial cells of the bronchial circulation and on airway epithelial cells. Thus, IL-4 increases the expression of the adhesion molecule, VCAM-1, on endothelial and airway epithelial cells and this may be important in eosinophil and lymphocyte trafficking.[45] IL-1 and TNF-α increase the expression of ICAM-1 in both vascular endothelium and airway epithelium.[46] Cytokines also play an important role in recruiting inflammatory cells to the airways (table 2).

Proliferation of myofibroblasts and the hyperplasia of airway smooth muscle may occur through the action of several growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-β). They may be released from inflammatory cells in the airways such as macrophages and eosinophils, but also by structural cells such as airway epithelium, endothelial cells, and fibroblasts. These growth factors may stimulate fibrogenesis by recruiting and activating fibroblasts or transforming myofibroblasts. Epithelial cells may release growth factors since collagen deposition occurs underneath the basement membrane of the airway epithelium.[47] Growth factors may also stimulate the proliferation and growth of airway smooth muscle cells. PDGF and epidermal growth factor (EGF) are potent stimulants of human airway smooth muscle proliferation[48][49] and these effects are mediated via activation of tyrosine kinase and protein kinase C. Growth factors may also be important in the proliferation of mucosal blood vessels and in the goblet cell hyperplasia that are characteristic of the chronically inflamed asthmatic airway. Cytokines such as TNF-α and fibroblast growth factors (FGF) may also play an important role in angiogenesis which is reported in chronic asthma.

Cytokine receptors
The receptors for many cytokines have now been cloned and, based on common homology

Table 2 Chemoattractant effects of cytokines

Cytokine	Eosinophil	T cell	Monocyte	Neutrophil	Others
IL-8	±			+++	"Primed" eosinophils
RANTES	++	Memory T cells	+		NK cells
MCP-1	+	+	++		Basophils
MCP-3	+	+	+		Dendritic cells
MCP-4	++	+	+		
MIP-1α		CD8+ cells	++		Dendritic cells, NK cells
Eotaxin	+++				Basophils
STCP-1		Th2 cells			–
IL-2	++				
IL-4					Fibroblasts
IL-5	+				
IL-15		+			
IL-16		CD4+ T cells			
IL-1β	(+)			++	
TNF-α				++	
SCF					Mast cells

IL = interleukin; MCP = monocyte chemoattractant protein; MIP = macrophage inflammatory protein; STCP = stimulated T cell chemoattractant protein; TNF = tumour necrosis; SCF = stem cell factor; NK = natural killer.
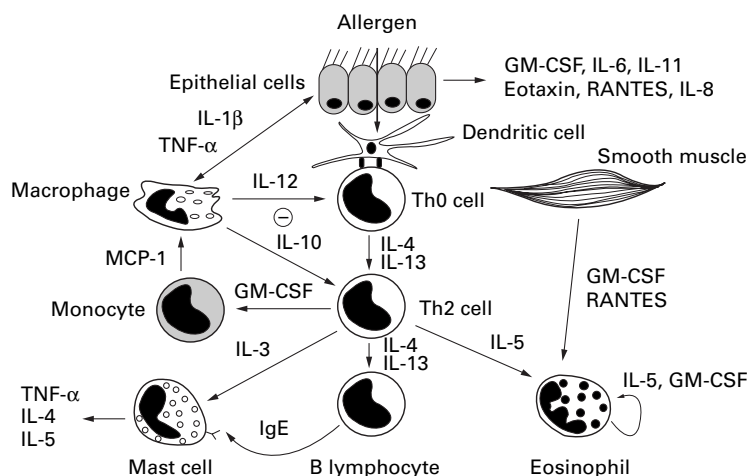
Figure 3   Interactions between resident and inflammatory cells and cytokines in the airways. For abbreviations, see text.

regions, these have been grouped into superfamilies.[50]

CYTOKINE RECEPTOR SUPERFAMILY

This large receptor superfamily includes IL-2R β and γ chains, IL-4R, IL-3R α and β chains, IL-5 α and β chains, IL-6R, gp130, IL-12R and GM-CSFR. The extracellular regions of the cytokine receptor family contain combinations of cytokine receptor domains, fibronectin type III domains and usually C2 immunoglobulin constant region-like domains. Some members are comprised of a single polypeptide chain which binds its ligand with high affinity. For other receptors there may be more than one binding affinity for the ligand, typically high and low binding affinity sites. Additional subunits have been identified which are required for high affinity receptor expression. Some of these subunits are shared by more than one cytokine receptor, giving rise to heterodimeric structures, such as receptors sharing the GM-CSF receptor β-chain (IL-3, IL-5 and GM-CSF), receptors sharing the IL-6 receptor β-chain, gp130 (IL-6, leukaemia inhibitory factor, oncostatin M), and receptors sharing the IL-2 receptor γ-chain (IL-2, IL-4, IL-7 and IL-15).

Cytokine receptors may be secreted as soluble forms produced by alternative splicing of their mRNA transcripts to produce proteins lacking the transmembrane region and the cytoplasmic proximal charged residues which anchor the protein into the membrane. They may act as agonists or antagonists or as transport proteins to carry cytokines to other sites.

IMMUNOGLOBULIN SUPERFAMILY

Cytokine receptors with immunoglobulin superfamily domains in their extracellular sequences include IL-1R, IL-6R, PDGFR, and M-CSFR. The immunoglobulin domains are characterised by a structural unit of about 100 amino acids, with a distinct folding pattern known as the immunoglobulin fold.

PROTEIN KINASE RECEPTOR SUPERFAMILY

These receptors have glycosylated extracellular ligand binding domains, a single transmembrane domain, and an intracellular tyrosine kinase catalytic domain. The superfamily includes receptors for growth factors such as PDGF, EGF, and FGF.

INTERFERON RECEPTOR SUPERFAMILY

This group includes IFN-α/β receptor, IFN-γ receptor, and IL-10 receptor. They are single spanning transmembrane glycoproteins, characterised by either one (IFN-γ and IL-10 receptors) or two (IFN-α/β receptors) homologous extracellular regions. Signal transduction involves phosphorylation and activation of JAK and TYK2 protein tyrosine kinases.

NERVE GROWTH FACTOR SUPERFAMILY

This includes cytokine receptors for NGFR, TNFR-I (p55), and TNFR-II (p75). These are characterised by three or four cysteine-rich repeats of about 40 amino acids in the extracellular part of the molecule. The mode of signal transduction has not been elucidated.

SEVEN TRANSMEMBRANE G PROTEIN COUPLED RECEPTOR SUPERFAMILY

These receptors include the chemokine receptors which have a characteristic structure of relatively short acidic extracellular N terminal sequence followed by seven transmembrane spanning domains with three extracellular and three intracellular loops. The receptors are coupled to heterotrimeric GTP binding proteins which induce phosphatidylinositol phosphate hydrolysis and activate kinases, phosphatases, and ion channels.

Cytokines in this review

Many cytokines are involved in the development of the atopic state and of the chronic inflammatory processes of asthma (fig 3), ultimately contributing to the release of mediators such as histamine and cys-LTs, airway remodelling, bronchoconstriction, and bronchial hyperresponsiveness. The potential role of each cytokine in these processes can be evaluated by studying their properties, their presence and localisation in the airway wall and airway secretions of patients with asthma, and the effect of specific inhibitors such as receptor antagonists or specific antibodies. Anti-inflammatory drugs for asthma may be developed by targeting inhibition of cytokine production and effects (such as cytokine antibodies, cytokine receptor antagonists, or blockers of specific signal transduction effects) or by using or modifying anti-inflammatory cytokines. We will consider each individual putative cytokine involved in asthma with regard to their synthesis and release, receptors, effects, and individual role in asthma and use the grouping proposed above. This is clearly necessary in order to appreciate the potential contribution of each cytokine and in view of the multiple functions that each cytokine has and that make one cytokine different from another. The potential role of each cytokine can be judged from its expression in asthmatic

airways, from studies in transgenic or knock-out mice, or from studies involving the use of inhibitors of synthesis or antibodies or blockers at the receptor level. This approach we have taken does not underestimate the fact that cytokines work as a network.

T cell derived cytokines (lymphokines)

INTERLEUKIN 2

Synthesis and release

Activated T cells, particularly Th0 and Th1 T cells, are a major source of IL-2,[51] while B lymphocytes can be induced under certain conditions to secrete IL-2 in vitro. IL-2 is secreted by antigen activated T cells following activation, accompanied later by an upregulation of high affinity IL-2 receptors on the same cells. Binding of IL-2 to IL-2R induces proliferation of T cells, secretion of cytokines, and enhanced expression of receptors for other growth factors such as insulin. The IL-2 receptor complex is then removed from the T cell surface by internalisation. IL-2 can also be produced by eosinophils[52] and by airway epithelial cells.[53]

Receptors

The IL-2 receptor complex is composed of three chains—α, β, and γ—and belongs to the family of haematopoietic cytokine receptors.[54 55] The α and β chains bind to IL-2 with low affinity while the γ chain does not bind IL-2 alone. The high affinity complex is a heterotrimer of α/β/γ, while α/γ and β/γ heterodimers have an intermediate affinity. The β chain, which is expressed constitutively in T lymphocytes, is essential for signal transduction and the intracellular domain has critical sequences necessary for growth promoting signals.[56] The γ chain also appears to be important for signal transduction[57] while the α chain alone is unable to transduce any signal.

Effects

IL-2 stimulates the growth and differentiation of T cells, B cells, natural killer (NK) cells, lymphokine activated cells, and monocytes/macrophages. IL-2 functions as an autocrine growth factor for T cells and also exerts paracrine effects on other T cells.[58] IL-2 is also involved in TcR stimulated T cell apoptosis.[59] It promotes the differentiation and immunoglobulin secretion of B cells. IL-2 acts on monocytes to increase IL-1 secretion, cytotoxicity, and phagocytosis.[58] Experiments with IL-2 gene knock out mice show that these animals develop a normal thymus and normal T cell subpopulations in peripheral tissues, indicating that IL-2 activity is redundant and not confined to IL-2 alone.[60] Together with IL-4, IL-2 can reduce glucocorticoid receptor binding affinity of blood mononuclear cells.[61] IL-2 stimulates NK cells to secrete IFN-γ, to proliferate and to increase cytolysis. IL-2 enhances the production of granulocyte-macrophage colony stimulating factor (GM-CSF) in peripheral blood mononuclear cells from asthmatics and IL-5 production from T cells from patients with the hypereosinophilic syndrome.[62 63] IL-2 is a potent chemoattractant for eosinophils in vitro.[64]

Infusion of IL-2 as part of chemotherapy treatment results in eosinophilia with an associated increase in eosinophil colony stimulating activity.[65 66] This activity was abolished by neutralising antibody to IL-3, IL-5 or GM-CSF, indicating that IL-2 is acting indirectly by promoting the synthesis of these cytokines. Repeated administration of IL-2 induces bronchial hyperresponsiveness in Lewis rats.[67] In ovalbumin sensitised Brown-Norway rats IL-2 caused a threefold increase in the late phase response compared with the response in rats receiving only saline prior to allergen exposure.[68] IL-2 caused an inflammatory response around the airways with a significant increase in eosinophils, lymphocytes, and mast cells.

Role in asthma

Levels of IL-2 are increased in bronchoalveolar lavage fluid of patients with symptomatic asthma.[13 69] Increased BAL cells expressing IL-2 mRNA are also present,[11] and a non-significant increase in IL-2 mRNA positive cells was observed in asthmatics following allergen challenge.[70] Particularly high levels of IL-2 and IL-4 mRNA positive bronchoalveolar lavage cells are observed in steroid resistant asthmatics compared with steroid sensitive asthmatics[71]; this increase is not abolished by pretreatment with oral prednisolone in the steroid resistant patients and there were no differences in the expression of IL-5 and IFN-γ mRNA between the two groups. IL-2R bearing T lymphocytes are increased in the circulating blood of patients with acute severe asthma and in bronchoalveolar lavage cells recovered from asthmatics after allergen exposure.[70 72]

Cyclosporin A, which inhibits IL-2 gene transcription in activated T lymphocytes through interference with the transcription factors AP-1 and NF-AT, inhibits allergic airway eosinophilia but not bronchial hyperresponsiveness in animal models.[73] However, in severe asthmatics cyclosporin A causes a reduction in the amount of oral steroid therapy needed to control asthmatic symptoms,[74] although not confirmed in another study.[75] These effects of cyclosporin A may derive from an inhibition of IL-2 expression as well as an inhibition of other cytokines such as GM-CSF and IL-5.

INTERLEUKIN 3

Synthesis and release

Activated helper T cells are the predominant sources of IL-3, together with mast cells.[76 77]

Receptors

The IL-3 receptor is formed by the association of a low affinity IL-3 binding α subunit (IL-3Rα) with a second β subunit which is common to the IL-5 and GM-CSF receptors but does not itself bind to these cytokines.[78] IL-3 binding to its receptor results in rapid tyrosine and serine/threonine phosphorylation of a number of cellular proteins including the IL-3Rβ subunit itself.[79 80] A monoclonal antibody to the IL-3Rα chain abolishes its function.[81] Human IL-3R is expressed on

myeloid, lymphoid, and vascular endothelial cells. It is selectively induced in human endothelial cells by TNF-α and potentiates IL-8 secretion and neutrophil transmigration.[82]

Effects

IL-3 is a pluripotential haematopoietic growth factor that, together with other cytokines such as GM-CSF, stimulates the formation of erythroid, megakaryocyte, neutrophil, eosinophil, basophil, mast cell, and monocytic lineages.[83] GM-CSF also increases the responsiveness of neutrophils to IL-3.[84] Mice that overexpress IL-3 only show modest eosinophilia but die early due to massive tissue infiltration and destruction by myeloid cells such as neutrophils and macrophages.[85]

Role in asthma

An increase in the number of cells expressing IL-3 mRNA has been reported in mucosal biopsy specimens and in bronchoalveolar lavage cells of patients with asthma.[11 86] However, after allergen challenge the numbers of IL-3 mRNA positive lymphocytes are not increased, in contrast to those expressing IL-5.[70]

INTERLEUKIN 4

Synthesis and release

IL-4 is derived from Th2 derived T lymphocytes and certain populations of thymocytes as well as eosinophils and cells of the basophil and mast cell lineage. Crosslinking of the CD40 ligand on human CD4+ T cells from normal non-allergic subjects generates a co-stimulatory signal that increases IL-4 synthesis.[87] Synthesis can also be induced by stimulation of the antigen receptor on T lymphocytes and by IgE Fc receptor crosslinking in mast cells and basophils. Interestingly, corticosteroids *enhance* the capacity to induce IL-4 synthesis from CD4+ T cells.[88] High affinity IL-4 receptors are abundant in activated B and T cells and are also present on haematopoietic progenitor cells, mast cells, macrophages, endothelial cells, epithelial cells, fibroblasts, and muscle cells.[89–91]

Receptors

The IL-4 receptor is a complex consisting of two chains, a high affinity IL-4 binding chain (p140, α chain) which binds IL-4 and transduces its growth promoting and transcription activating functions[92 93] and the IL-2R γ chain (the common γ chain, γc) which amplifies signalling of the IL-4R.[94 95] The α chain belongs to the cytokine receptor superfamily. A recombinant extracellular domain of the human IL-4R is a potent IL-4 antagonist.[96] The IL-2R γ chain augments IL-4 binding affinity.[94 95] A low affinity IL-4 receptor has also been identified.[97] High affinity IL-4 receptors are abundant in activated B and T cells. They are also present on haematopoietic progenitor cells, mast cells, macrophages, endothelial cells, epithelial cells, fibroblasts, and muscle cells.[89–91] Expression of the α subunit of the IL-4R has been localised to the airway epithelium, T cells, and mast cells in the airway mucosa, with greater expression in bronchial biopsy specimens from asthmatic subjects.[98]

IL-4 induces phosphorylation of the IL-4 induced phosphotyrosine substrate, which is associated with the p85 subunit of phosphatidylinositol-3 kinase and with Stat-6 and Janus protein kinase (JAK) after cytokine stimulation.[99–102] The transcription factor Stat-6 is essential for mediating the effects of IL-4.[103 104] IL-4 also stimulates phosphoinositol phosphate-2 hydrolysis, yielding IP_3 and subsequent calcium flux followed by increased intracellular cAMP.[105] Interestingly, an association with atopy has been found with a R567 allele of the IL-4R α subunit[106] which enhances signalling and decreases the binding of the phosphotyrosine phosphatase SHP-1 implicated in termination of signalling by means of cytokine receptors.[102 107]

Effects

IL-4 plays an important role in B lymphocyte activation by increasing expression of class II MHC molecules as well as enhancing expression of CD23, the low affinity (FcεRII) receptor, CD40 and the α chain of the IL-2 receptor. It promotes immunoglobulin synthesis by B lymphocytes and plays a central role in immunoglobulin class switching of activated B lymphocytes to the synthesis of IgG4 and IgE. This switching is accompanied by germline ε chain synthesis. IL-4 promotes the development of Th2-like CD4 T cells and inhibits the development of Th1-like T cells.[108 109] It also enhances the cytolytic activity of CD8 cytotoxic T cells. Virus-specific CD8+ T cells can be induced by IL-4 to produce IL-5.[110]

IL-4 also exerts effects on monocytes and macrophages. It enhances the surface expression of MHC class II molecules and the antigen presenting capacity of macrophages, but inhibits the macrophage colony formation and cytokine release of TNF, IL-1, IL-12, IFN-γ, IL-8, and macrophage inflammatory protein 1α (MIP-1α). Together with other cytokines such as G-CSF and IL-6, IL-4 can promote the growth of mast cell and myeloid and erythroid progenitors. IL-4 also upregulates endothelial VCAM-1 expression on the endothelium. Interaction of VCAM-1 with the very late activation antigen 4 (VLA-4) promotes eosinophil recruitment.[45] IL-4 also induces fibroblast chemotaxis and activation[111 112] and, in concert with IL-3, IL-4 promotes the growth of human basophils and eosinophils.[113]

IL-4 has inhibitory effects such as suppression of metalloproteinase biosynthesis in human alveolar macrophages,[114] inhibition of the expression of inducible nitric oxide synthase in human epithelial cells,[115] and reduction of RANTES and IL-8 expression in human airway smooth muscle cells.[116 117]

Role in asthma

IL-4 is expressed by CD4+ and CD8+ T cells, eosinophils, and mast cells in both atopic and non-atopic asthma.[118 119] Increased numbers of lymphocytes expressing IL-4 mRNA together

with IL-5 mRNA in bronchoalveolar lavage cells are observed following allergen challenge.[86] The potential importance of IL-4 in inducing allergic airway inflammation has been addressed in IL-4 knock out mice. Sensitisation and exposure to ovalbumin did not induce lung eosinophilia as it did in the wild type litter mates.[120] No ovalbumin specific IgE was observed on active sensitisation and repeated exposures to ovalbumin did not induce bronchial hyperresponsiveness.[121] IL-4 appears crucial to Th2 cell development. In IL-4 knock out mice T cells recovered from the airways do not synthesise a Th2 cytokine pattern, correlating with the absence of inflammatory airway changes.[122] When wild type mice are treated with an anti-IL-4 antibody during the exposure to aerosolised ovalbumin but not during the sensitisation process, the influx of eosinophils to the airways is not inhibited.[122 123] IL-4 receptor blockade prevented the development of antigen induced airway hyperresponsiveness, goblet cell metaplasia, and pulmonary eosinophilia in a mouse model.[124] Inhalation of IL-4 by asthmatics causes an increase in eosinophil numbers in induced sputum, together with a transient increase in bronchial responsiveness.[125] IL-4 overexpression in mouse airways induces mucin MUC5AC gene expression and mucin hypersecretion, indicating a potential role for IL-4 in mucus hypersecretion.[126]

INTERLEUKIN 5
Synthesis and release
IL-5 was first isolated from supernatants of activated murine spleen cells which were shown to induce eosinophil colony formation. The isolated soluble activity was shown to stimulate eosinophil production from murine bone marrow selectively and was termed eosinophil differentiation factor. IL-5 was isolated from this soluble activity.[127] It is produced by T lymphocytes and an increased expression of IL-5 mRNA has been demonstrated in CD4+ T cells in asthmatic airways using in situ hybridisation.[128] Bronchoalveolar lavage CD4+ and CD8+ T cells can also secrete IL-5.[129] Human eosinophils can express IL-5 mRNA and release IL-5 protein in vitro[130] and endobronchial challenge results in IL-5 mRNA expression in eosinophils in BAL fluid[131] with an increase in IL-5 concentrations of up to 300-fold.[132 133] Raised IL-5 concentrations have been reported in BAL fluid from symptomatic but not asymptomatic asthmatic subjects.[134] Increased circulating levels of immunoreactive IL-5 have been measured in the serum of patients with exacerbations of asthma and these levels fall with corticosteroid treatment.[135] IL-5 levels are raised in induced sputum following allergen challenge of asthmatic patients.[136] IL-5 protein has also been localised by immunochemistry in mast cells in bronchial biopsy specimens of patients with asthma together with IL-4, IL-6, and TNF-α.[21] The transcriptional control of the human IL-5 gene involves several transcription factors including NF-AT.[137]

Receptors
The human IL-5R has been identified in vitro on eosinophils but not on neutrophils or monocytes.[138] It consists of a heterodimer with two polypeptide chains, a low affinity binding α chain and a non-binding β chain shared with the IL-3R and GM-CSFR.[139] Both chains belong to the cytokine receptor superfamily.[140] The α subunit alone is sufficient for ligand binding and is specific for IL-5, but association with the β chain leads to a 2–3-fold increase in binding affinity and allows signalling to occur. Some IL-5R mutants have antagonistic effects and may act as receptor antagonists.[141] Transcriptional regulation of the specific chain yields either membrane bound or soluble forms of the receptor (IL-5Rm and IL-5Rs).[142] The membranous form interacts with the β subunit, leading to a substantial increase in affinity for IL-5.[143] The soluble form is secreted in body fluids and interacts with IL-5 and antagonises the action of IL-5 on target cells.[142 144] The expression of IL-5R is restricted to eosinophils and their immediate precursors. The number of cells in bronchial biopsy specimens from asthmatic subjects expressing both forms of the receptor is increased, with the expression of IL-5R mRNA being predominantly in eosinophils.[145] An increase in membrane bound IL-5R mRNA on bone marrow progenitor cells (CD34+) occurs following allergen challenge of atopic asthmatic subjects.[146]

There are two major signalling pathways of IL-5 in eosinophils. IL-5 activates the tyrosine kinases Lyn, Syk and JAK2 and propagates signals through the Ras-MAPK and JAK-STAT pathways. For eosinophil survival Lyn, Syk and JAK2 tyrosine kinases and SHP-2 tyrosine phosphatase are important, while for eosinophil degranulation and adhesion molecule expression Raf-1 kinase is critical.[147]

Effects
IL-5 can influence the production, maturation, and activation of eosinophils. It acts predominantly at the later stages of eosinophil maturation and activation[148 149] and can also prolong the survival of eosinophils.[150] IL-5 appears to be the main cytokine involved in the development of eosinophilia in vivo. Administration of exogenous IL-5 causes eosinophilia in many in vivo models.[151] IL-5 transgenic mice in which transcription of IL-5 is coupled to the dominant control region of the gene encoding for the constitutive marker CD2 show lifelong eosinophilia in organs with predicted T cell expression such as bone marrow, spleen and peritoneum, with fewer cells in the airway mucosa.[85] IL-5 transgenic mice behave normally, indicating that eosinophils need other factors for degranulation and subsequent tissue damage. Thus, intratracheal administration of another eosinophil chemotactic agent, eotaxin, leads to further eosinophil accumulation in the lungs with bronchial hyperresponsiveness, an effect not observed in wild type mice.[152] IL-5 may cause eosinophils to be released from the bone marrow while local release of another chemoattractant may be necessary to cause tissue localisation of eosinophils.[32] On the other

hand, IL-5 instilled into the airways of patients with asthma induce significant airway eosinophilia[153] and inhaled IL-5 caused eosinophilia in induced sputum and bronchial hyperresponsiveness but had no effect on airway calibre[154]. The eosinophilotactic responses of BAL fluid of asthmatics during the pollen season is accounted for by IL-5 and RANTES.[155]

Role in asthma
IL-5 may play an important part in eosinophil maturation, chemoattraction, and activation in asthma, and may underlie bronchial hyperresponsiveness. It may also interact with other eosinophil chemoattractants and activators such as chemokines to activate and induce chemoattraction of eosinophils.[32 156] The expression of IL-5 in tissues and cells from patients with asthma is discussed above. Studies with IL-5 monoclonal antibodies clearly support a role for IL-5 in asthma. Pretreatment with anti-IL-5 monoclonal antibodies can suppress allergen induced airway eosinophilia.[157–160] There is some debate about whether the IL-5 induced eosinophilia is the direct cause of bronchial hyperresponsiveness induced by allergen exposure. In some studies there is an effect of anti-IL-5 antibodies on bronchial hyperresponsiveness,[157 159] while such an effect is not reported in another study despite inhibition of eosinophilia.[123] In IL-5 knock out mice both allergen induced eosinophilia and airway hyperresponsiveness are abolished.[161] The site of IL-5 expression may be critical to eosinophil recruitment and the development of airway hyperresponsiveness. Transgenic mice overexpressing IL-5 in lung epithelial cells showed raised levels of IL-5 in BAL fluid and serum, lung histopathological changes reminiscent of asthma, and display baseline airway hyperresponsiveness.[162] On the other hand, studies in mice indicate that circulating but not local lung IL-5 is required for the development of antigen induced airways eosinophilia.[163] Indeed, sensitisation and allergen challenge of mice leads to an increase in IL-5 producing T cells in the bone marrow.[164] In addition to its effect in mobilising eosinophils from the bone marrow, there is evidence for its effect as a regulator of eosinophil homing and migration into tissues in response to local chemokine release.[165]

Studies of anti-IL-5 antibodies in human asthma are currently under way. In patients with worsening asthma, systemic corticosteroids reduces the expression of IL-5 mRNA in the airways mucosa associated with an improvement in asthma.[166] Cyclosporin A and tacrolimus (FK506), immunosuppressant agents sometimes used in the treatment of severe asthma, inhibit the expression of IL-5 mRNA in activated human T lymphocytes in response to phytohaemagglutinin or phorbol esters.[167]

INTERLEUKIN 9
Synthesis and release
IL-9, originally identified as a T cell growth factor,[168] is a T cell derived cytokine with pleiotropic effects on many cell types.[169] It is produced in vitro and in vivo by CD4+ T cells, preferentially by the Th2 subset.[170–173]

Effects
IL-9 can stimulate the proliferation of activated T cells,[168 174 175] enhance the production of immunoglobulins including IgE in B cells,[176] and promote the proliferation and differentiation of mast cells[177 178] and of haematopoietic progenitors.[179 180] It strongly synergises with stem cell factor for the growth and differentiation of mast cells.[181] IL-9 may upregulate the expression of mast cell proteases including the monocyte chemoattractant proteins mMCP-1, mMCP-2, mMCP-4[178] and granzyme B.[182] It may be involved in lymphomagenesis.[183]

Role in asthma
Transgenic mice created by expression of IL-9 regulated by a rat Clara cell 10 protein promoter showed lung selective expression of IL-9 with massive infiltration with eosinophils and lymphocytes, and increased numbers of mast cells within the airway epithelium.[184] Epithelial cell hypertrophy associated with accumulation of mucus-like material within nonciliated cells and increased subepithelial deposition of collagen was also observed. The mice also demonstrated marked bronchial hyperresponsiveness with normal baseline airway calibre.[184] In another IL-9 transgenic mouse, eosinophilic airway inflammation, increased serum IgE levels, and bronchial hyperresponsiveness were observed.[185]

IL-9 has been suggested as a candidate gene predisposing to asthma on the basis of linkage disequilibrium between serum total IgE levels and a marker within the IL-9 gene which is situated on the 5q31-q33 chromosome.[186] In inbred strains of mice, IL-9 has been identified as a factor regulating bronchial hyperresponsiveness.[187] The human IL-9 receptor has been proposed as another potential asthma gene candidate[188] and there are non-functional transcripts of IL-9 receptors.[189]

INTERLEUKIN 13
Synthesis and release
IL-13 is synthesised by activated CD4+ and CD8+ T cells and is a product of Th1-, Th2-, and Th0-like CD4 T cell clones.[190] Both CD4+ and CD8+ T cell clones synthesise IL-13 in response to antigen specific or polyclonal stimuli.[191]

Receptors
There is a close similarity between IL-4 and IL-13 receptors. An IL-4 receptor antagonist derived from a mutant protein[192] is a potent receptor antagonist of the biological activity of IL-4 and also of IL-13. It particularly inhibits the effect of IL-13 in inducing IgE synthesis in peripheral blood mononuclear cells. There is evidence from cDNA cloning of the IL-13 receptor to suggest that the IL-4R α chain is a component of IL-13R.[193] However, despite this, these receptors appear to be distinct.[191]

Effects

IL-13 is a potent modulator of human monocyte and B cell function.[190] It has profound effects on human monocyte morphology, surface antigen expression, antibody dependent cellular toxicity, and cytokine synthesis.[190 194] IL-13, like IL-4, upregulates the expression of β_1-integrin and VCAM-1 and the production of IL-6 and MCP-1 from human lung fibroblasts.[195] On the other hand, in human monocytes stimulated by lipopolysaccharide, the production of proinflammatory cytokines, chemokines and colony-stimulating factors (IL-1β, IL-6, IL-8, IL-10, IL-12, IFN-γ, and GM-CSF) is inhibited by IL-13, while IL-1ra secretion is increased.[196–198] MIP-1α, IL-1 and TNF-α release is inhibited from human alveolar macrophages.[198 199] IL-13 inhibits the release of RANTES and IL-8 from airway smooth muscle cells in vitro.[116 117] These actions of IL-13 are similar to those of IL-4 and IL-10. The suppressive effects of IL-13 and of IL-4 are not related to endogenous production of IL-10. Similar to IL-4, IL-13 decreases the transcription of IFN-γ and of IL-12. It is possible that IL-13 acts like IL-4 and suppresses the development of Th1 cells by downregulating IL-12 production by monocytes, thereby favouring the development of Th2 cells.[108 109 200] IL-13, unlike IL-4, fails to activate human T cells which appears to be due to a lack of IL-13 receptors on these cells. IL-13 diminishes monocyte glucocorticoid receptor binding affinity.[201] It activates eosinophils by inducing the expression of CD69 cell surface protein and prolonging eosinophil survival.[202]

IL-13 induces the expression of CD23 on purified human B cells and acts as a switch factor directing IgE synthesis, similar to IL-4.[203 204] A potent receptor antagonist of the biological activity of IL-4, a mutant protein of IL-4, antagonises IL-13 actions such as blocking the proliferation of B cells and IgE synthesis.[205] This mutant protein of IL-4 may therefore have therapeutic potential for the treatment of allergies.

Role in asthma

An increased expression of IL-13 mRNA has been reported in the airway mucosa of patients with atopic and non-atopic asthma.[206 207] In addition, levels of IL-13 together with IL-4 increased following segmental allergen challenge of patients with asthma.[208] There is a significant correlation between the eosinophil counts and the levels of IL-13. A cloned piece of soluble IL-13a2-IgGfc fusion protein that specifically binds to and neutralises IL-13 without affecting IL-4 suppresses the increase in mucus secretion, eosinophilia and bronchial hyperresponsiveness following allergen exposure in sensitised mice.[209 210] IL-13 administered to mice increases airway eosinophilia and bronchial hyperresponsiveness. IL-13 is therefore independently involved in the mouse sensitised model.

INTERLEUKIN 15

Synthesis and release

IL-15 is produced by both CD4+ and CD8+ T cells after activation.[211] IL-15 mRNA is expressed in lung fibroblasts and epithelial cell lines as well as monocytes and human blood-derived dendritic cells.[212]

Effects

IL-15 shares some of the properties of IL-2, such as the stimulation of proliferation of T cells and lymphokine activated natural killer cells. However, there are many other distinct effects of IL-15. IL-15 can induce IL-8 and MCP-1 production in human monocytes.[213] It also induces the release of soluble IL-2Rα from human blood mononuclear cells.[214] It promotes angiogenesis in vivo[215] and can also activate neutrophils and delay their apoptosis.[216] IL-15 promotes the synthesis of IL-5 from house dust mite specific human T cell clones,[217] an effect inhibited by the tyrosine kinase inhibitor, herbimycin A. This indicates that IL-15 produced at the site of allergic inflammation may play a part in recruitment and activation of eosinophils by inducing IL-5 production from T cells. IL-15 is also a chemoattractant for human blood T lymphocytes, an effect inhibited by an anti-IL-2R β chain antibody.[218]

Role in asthma

There are no data specific to asthma.

INTERLEUKIN 16

Synthesis and release

IL-16, previously known as lymphocyte chemoattractant factor, was first identified as a product of peripheral blood mononuclear cells following mitogen and histamine stimulation in vitro.[219 220] Subsequently, it was shown to be produced by CD8+ T cells following stimulation with histamine and serotonin in vitro.[221 222] IL-16 can also be produced by epithelial cells,[223] eosinophils,[224] and mast cells.[225]

Effects

IL-16 has specific activities on CD4+ T cells.[226] It selectively induces migration of CD4+ including CD4+ T cells and CD4-bearing eosinophils.[227] IL-16 acts as a growth factor for CD4+ T cells and induces IL-2R and MHC class II molecules on these cells.[228]

Role in asthma

Increased concentrations of IL-16 have been found in BAL fluid obtained from asthmatic subjects following allergen and histamine challenge.[229 230] In stable atopic asthmatic subjects there is predominant expression of IL-16 mRNA and immunoreactivity in airway epithelium.[231] In the ovalbumin sensitised and exposed mouse model IL-16 immunoreactivity was detected in the airway epithelium and an anti-IL-16 antibody prevented OVA specific IgE responses, bronchial hyperresponsiveness, but not airway eosinophilia.[232]

INTERLEUKIN 17

IL-17 is a CD4+ T cell derived cytokine which stimulates NF-κB and IL-6 production in

fibroblasts and co-stimulates T cell proliferation.[233] It stimulates epithelial, endothelial, and fibroblastic cells to secrete cytokines such as IL-6, IL-8 and GM-CSF, and PGE$_2$.[234][235] In the presence of IL-17, fibroblasts can sustain the proliferation of CD34+ haematopoietic progenitors and their preferential maturation into neutrophils. IL-17 increases the release of NO in cartilage from patients with osteoarthritis via NF-κB activation.[236]

INTERLEUKIN 18
IL-18 or IFN-γ-inducing factor (IGIF) is a cytokine which is a potent inducer of IFN-γ production and plays an important part in Th1 responses.[237] Human IL-18 has been cloned from normal human liver cDNA libraries using murine IL-18 cDNA clones. IL-18 is synthesised as a precursor molecule without a signal peptide, but requires the IL-1-converting enzyme (ICE, caspase-1) for cleavage into a mature peptide. The human IL-18 receptor has been recently purified and characterised. Human IL-1 receptor protein is a functional IL-18 receptor component.[238] IL-18 receptors are expressed selectively on murine Th1 cells but not on Th2 cells.[239]

Recombinant human IL-18 induces IFN-γ production by mitogen stimulated peripheral blood mononuclear cells and enhances natural killer (NK) cell cytotoxicity, increases GM-CSF production, and decreases IL-10 production. IL-18 induces IL-8, MIP-1α, and MCP-1 in human peripheral blood mononuclear cells in the absence of any co-stimuli. It directly stimulates gene expression and synthesis of TNF-α from CD3+/CD4+ T cells and NK cells, with the subsequent production of IL-1β and IL-8 from CD14+ monocytes.[240] IL-18 induces phosphorylation of p56 (1ck) and mitogen activated protein kinase, and these may be involved in TCR/CD3 mediated responses.[241] IL-18 also activates NF-κB in murine Th1 cells for enhancement of IL-2 gene expression by Th1 cells.[242] IL-18, together with IL-12, induces anti-CD40 activated B cells to produce IFN-γ, which inhibits IL-4 dependent IgE production.[243] IL-18 and IL-12 have synergistic effects on Th1 development which may be due to reciprocal upregulation of their receptors.[239]

Pro-inflammatory cytokines
INTERLEUKIN 1
Synthesis and release
There are two forms of IL-1 (α and β) derived from two different genes. Although the amino acid sequence homology between human IL-1α and IL-1β is only 20%, the molecules bind to the same receptor and have nearly identical properties. IL-1β (17.5 kDa) is synthesised as a larger precursor molecule with a molecular weight of 31 kDa and is released into the extracellular space and the circulation. The most active form of IL-1β is its cleaved mature form resulting from the action of a specific cysteine protease, IL-1 converting enzyme.[244][245]

IL-1 is produced by a variety of cells including monocytes/macrophages, fibroblasts, B cells, both Th1 and Th2-like T cell lines, NK cells, neutrophils, endothelial cells, epithelial cells, airway smooth muscle cells, and vascular smooth muscle cells. The major source of IL-1 in most tissues is the stimulated monocyte/macrophage. Monocytes produce 10 times as much IL-1β as IL-1α,[246][247] and IL-1α is mainly cell associated while IL-1β is mostly released. Eosinophils can produce IL-1α[248] while human epithelial cells can augment IL-1β expression when exposed to the air pollutant nitrogen dioxide.[249] A wide variety of stimuli including IL-1 itself,[250] TNF-α,[251] GM-CSF,[252] endotoxin, and phagocytosis can increase the expression of IL-1 in monocytes/macrophages. IL-1 production by endothelial and vascular smooth muscle cells can be induced also by IL-1, TNF, or endotoxin. On the other hand, PGE$_2$ and corticosteroids can attenuate the capacity of endotoxin and other stimuli to release IL-1 through an inhibition of transcription and through a decrease in IL-1 mRNA stability.[253–255] An inhibitor of the IL-1 converting enzyme inhibits inflammatory responses to IL-1β.[256]

Receptors
Two IL-1 receptors have been described. The type I receptor (CDw121a) and type II receptor (CDw121b) are transmembrane glycoproteins that bind IL-1α, IL-1β, and IL-1ra. IL-1R1 is expressed on many cells including T cells, B cells, monocytes, NK cells, basophils, neutrophils, eosinophils, dendritic cells, fibroblasts, endothelial cells, and vascular endothelial cells while IL-R2 is also expressed on T cells, B cells and monocytes. An IL-1R accessory protein (IL-1R-AcP) has been described[257] which, when associated with IL-1R1, increases its affinity for IL-1β. Only IL-1R1 transduces a signal in response to IL-1,[258] while IL-1R2 on binding to IL-1 does not. Thus, IL-1R2 may act as a decoy receptor, preventing IL-1 from binding to IL-1R1.[259] IL-1 signal transduction pathways are associated with TNF receptor associated (TRAF) adaptor proteins, particularly TRAF-6.[260] TRAF-6 associates with IL-1 receptor associated kinase (IRAK) which is recruited to and activated by the IL-1 receptor complex.[261]

A soluble receptor found in normal human serum and secreted by the human B cell line RAJI which binds preferentially to IL-1β has been described.[262] IL-1 downregulates the numbers of IL-1 receptors[263][264] while PGE$_2$ increases the expression of IL-1 receptors.[265][266] PDGF can increase IL-1 receptor expression and IL-1 receptor mRNA in fibroblasts,[267][268] while IL-4 increases receptor expression on T cells.[269] TGF-β may decrease the expression of IL-1 receptors,[270] and may also uncouple the response of the cells to IL-1 without affecting IL-1 receptor expression or binding of IL-1.[271]

Some of the effects of IL-1 can be mimicked by agents that increase cAMP and activate protein kinase A,[272][273] while others can be mimicked by agents that activate protein kinase C (PKC).[274–276] Many cells produce cAMP in response to IL-1. Activation of protein kinase A by an IL-1 induced increase in cAMP may lead

to increased transcription of a certain number of cellular genes. These may activate activating transcription factors (ATF) that bind to a *cis*-acting cAMP responsive element[277] and NF-κB through the phosphorylation of an inhibitor protein, IκB. AP-1 activity may also be induced by IL-1[278] through activation of PKC. Phosphorylation of several cellular proteins through the action of PKC independent serine/threonine kinase may also occur on activation of IL-1 receptor.[279]

Effects
IL-1 induces fever similar to other endogenous pyrogens such as TNF and IL-6. It partly causes leucocytosis by release of neutrophils from the bone marrow and induces the production of other cytokines including IL-6.

IL-1 is a growth factor for mature and immature thymocytes and a co-factor in the induction of proliferation and IL-2 secretion by peripheral blood CD4 and CD8 T cells following engagement of their antigen receptors. IL-1β is an important growth factor for Th2 cells in response to antigen primed antigen presenting cells but not for Th1 cells.[280] Synergistic effects between IL-1 and IL-6 have been reported for the activation of T cells.[281–283] It also functions as a growth factor for B cells.[284–286] IL-1 induces the induction of many other cytokines such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, RANTES, GM-CSF, IFN-γ, PDGF, and TNF from a variety of cells. It induces fibroblasts to proliferate,[287] an effect that may be due to release of PDGF,[288] increases prostaglandin synthesis and collagenase secretion,[263 289] and increases the synthesis of fibronectin and types I, III, and IV collagen.[290] Together with TNF-α and IFN-γ, IL-1β can induce or upregulate the expression of ICAM-1 and VCAM-1 on endothelial cells and also on respiratory epithelial cells which may lead to increased adhesion of eosinophils to the vascular endothelium and respiratory epithelium.[291 292] IL-1 induced adhesion of eosinophils to endothelial cell monolayers is inhibited by anti-ICAM and anti-VCAM antibodies.[293]

Role in asthma
Levels of IL-1β in BAL fluid of patients with asthma were found to be increased compared with those of non-asthmatic volunteers, together with an increase in IL-1β specific mRNA transcripts in BAL fluid macrophages.[294] In addition, patients with symptomatic asthma show increased levels of IL-1β in BAL fluid compared with patients with asymptomatic asthma.[13] Increased expression of IL-1β in asthmatic airway epithelium has been reported, together with an increased number of macrophages expressing IL-1β.[295] Selective inhibition of IL-1β expression in the epithelium of the airway wall, without a reduction in IL-1ra expression after corticosteroid therapy, has been described in patients with asthma.[296]

IL-1β induces airway neutrophilia and increases airways responsiveness selectively to bradykinin in the rat.[297] IL-1β can induce eosinophil accumulation in rat skin, an effect blocked by an anti-IL-8 antibody.[298] Of interest, IL-1β has profound effects on the coupling of the β$_2$ adrenergic receptor to adenylyl cyclase, an effect mediated through the upregulation of inhibitory G proteins[299] and the induction of cyclo-oxygenase 2 enzyme.[300]

TUMOUR NECROSIS FACTOR α (TNF-α)
Synthesis and release
Two major forms of TNF exist—TNF-α and TNF-β—which have only 35% amino acid homology but bind to similar receptors. TNF-α (previously known as cachectin) is expressed as a type II membrane protein attached by a signal anchor transmembrane domain in the propeptide.[301] TNF-α is released from cells by proteolytic cleavage of the membrane bound form by a metalloproteinase, TNF-α converting enzyme (TACE). Inactivation of the TACE gene compromises the ability of cells to produce soluble TNF-α. TNF-α is produced by many cells including macrophages, T lymphocytes, mast cells, and epithelial cells, but the principal source is the macrophage. The secretion of TNF-α by monocytes/macrophages is greatly enhanced by other cytokines such as IL-1, GM-CSF and IFN-γ. Human eosinophils are also capable of releasing TNF-α,[302] together with airway epithelial cells.[303] TNF-β is mainly produced by activated lymphocytes.

Receptors
TNF-α interacts with two cell surface receptors, TNF-R55 and TNF-R75. Both receptors are members of the nerve growth factor receptor superfamily. Soluble p55 and p75 receptors have been described and are derived from the extracellular domain of each receptor. They may act as inhibitors of the effects of TNF.[304] TNF receptors are distributed on nearly all cell types except red blood cells and resting T lymphocytes. The p75 receptor is more restricted to haematopoietic cells. TNF-R75 is the principal receptor released by human alveolar macrophages and monocytes in the presence of IFN-γ.[305]

Several signalling pathways leading to activation of different transcription factors such as NF-κB and AP-1 have been identified. The TNF receptor associated factor (TRAF) family of adaptor proteins, particularly TRAF-2, are involved in signalling from the TNF receptors.[306] TRAF-2 may also have a role in the signal transduction pathway from the TNF receptor to the activation of mitogen activated protein (MAP) kinase cascades with subsequent activation of NF-κB and AP-1. TNF activates a sphingomyelinase resulting in the release of ceramide from sphingomyelin which in turn activates a Mg^{++} dependent protein kinase.[307]

Effects
Many of the actions of TNF-α occur in combination with other cytokines as part of the cytokine network and the effects of TNF-α are very similar to those of IL-1β as there is close interaction in the signal transduction pathway of

these two cytokines.[308] TNF-α potently stimulates airway epithelial cells to produce cytokines including RANTES, IL-8 and GM-CSF,[309–311] and also increases the expression of the adhesion molecule ICAM-1.[46] TNF-α also has a synergistic effect with IL-4 and IFN-γ to increase VCAM-1 expression on endothelial cells.[312] This would have the effect of increasing the adhesion of inflammatory leucocytes such as neutrophils and eosinophils at the airway surface. TNF-α enhances the expression of class II MHC molecules on antigen presenting cells. In addition, it enhances the release of IL-1 by these cells. It also acts as co-stimulatory factor for activated T lymphocytes, enhancing proliferation and expression of IL-2 receptors. TNF-α inhibits bone resorption and synthesis and induces proliferation of fibroblasts.[313] It also stimulates bronchial epithelial cells to produce tenascin, an extracellular matrix glycoprotein.[314]

Role in asthma
TNF-α may have an important amplifying effect on asthmatic inflammation.[315 316] There is evidence of increased expression in asthmatic airways[317] and IgE triggering in sensitised lungs leads to increased expression in epithelial cells in both rat and human lung.[318 319] Increased TNF-α mRNA expression in bronchial biopsy specimens of asthmatic patients has been reported.[320] TNF-α is also present in the BAL fluid of asthmatic patients[13] and TNF-α release from bronchoalveolar leucocytes of asthmatic patients is increased.[321] TNF-α is also released from alveolar macrophages of asthmatic patients after allergen challenge.[322] Furthermore, both blood monocytes and alveolar macrophages show increased gene expression of TNF-α after IgE triggering in vitro and this effect is enhanced by IFN-γ.[323] Alveolar macrophages of asthmatic patients undergoing late phase responses after allergen challenge release more TNF-α and IL-6 ex vivo than those from patients with only an early response.[322] There are polymorphisms in the promoter of the TNF gene which may be more frequently associated with asthma.[324 325]

TNF-α increases airway responsiveness in Brown-Norway rats[326] and in humans in association with an increase in sputum neutrophils.[327] It may be an important mediator in initiating chronic inflammation by activating the secretion of cytokines from a variety of cells in the airways. Several approaches to inhibition of TNF-α synthesis of effects are now under investigation in asthma, including monoclonal antibodies to TNF and soluble TNF receptors.

INTERLEUKIN 6
Synthesis and release
IL-6 was originally described for its antiviral activity, its effects on hepatocytes, and its growth promoting effects on B lymphocytes and plasmacytomas. It is secreted by monocytes/macrophages, T cells, B cells, and other cells including fibroblasts, bone marrow stromal cells, keratinocytes, and endothelial cells. Epithelial cells also appear to produce IL-6.[328] Human airway smooth muscle cells under activation with IL-1β or TGF-β can release IL-6.[329] Major basic protein secreted from eosinophils can interact with IL-1 or TGF to increase IL-6 release from fibroblasts.[330] IL-6 has also been localised to eosinophil granules.[331]

Effects
IL-6 is a pleiotropic cytokine whose role in asthma remains unclear. It has growth regulatory effects on many cells and is involved in T cell activation, growth, and differentiation. It is a terminal differential factor for B cells and induces immunoglobulin (IgG, IgA and IgM) secretion.[332] IL-6 is an important co-factor in IL-4 dependent IgE synthesis.[333] It upregulates the production of, and its response to, IL-2.

IL-6 may also have anti-inflammatory effects. It inhibits the expression and release of IL-1 and TNF from macrophages in vitro and endotoxin induced TNF production and neutrophil influx in the airways in vivo.[334–336] In IL-6 transgenic mice there is a lymphocytic infiltration around airways associated with reduced airways responsiveness.[337]

Role in asthma
There is increased release of IL-6 from alveolar macrophages from asthmatic patients after allergen challenge[322] and increased basal release compared with non-asthmatic subjects.[13] IgE dependent triggering stimulates the secretion of IL-6 in both blood monocytes and alveolar macrophages in vitro.[323] Increased levels of IL-6 can be measured in nasal washings of children following a rhinovirus infection.[14] In addition, IL-6 mRNA expression with increased NFκB-DNA binding activity can be induced by rhinovirus infection of cells in vitro.[14]

INTERLEUKIN 11
Synthesis and release
IL-11, which is distantly related to IL-6, is produced by fibroblasts, epithelial cells and human airway smooth muscle cells when stimulated by IL-1 and TGF-β$_1$.[329 338] A single class of specific receptor has been described on mouse cells.[339]

Receptors
The receptor has not yet been cloned. Like IL-6, IL-11 uses the IL-6 signal transducer gp130. On ligand binding, phosphorylation of tyrosine residues in a number of proteins occurs.[340 341]

Effects
Although IL-11 cDNA was cloned on the basis of IL-6-like bioactivity, IL-11 has distinct biological features from IL-6. IL-11 promotes multiple stages of human megakaryocytopoeisis and thrombopoeisis. In combination with stem cell factor or IL-4, IL-11 supports the generation of B cells, similar to IL-6.[342] IL-11 induces the production of acute phase reactants[343] and induces the synthesis of tissue inhibitor of metalloproteinase 1. It inhibits IL-12 and TNF-α production from

monocytes/macrophages,[344] effects mediated at the transcriptional level by inhibition of NF-κB.

Role in asthma

IL-11 can be detected in BAL fluid during upper respiratory viral infections in humans and induces non-specific bronchial hyperresponsiveness in mice.[345] Targeted expression of IL-11 in mouse airways leads to a T cell inflammatory response with airway remodelling, local accumulation of myofibroblasts, and airways obstruction.[346]

GRANULOCYTE–MACROPHAGE COLONY STIMULATING FACTOR (GM-CSF)

Synthesis and release

GM-CSF is one of the colony stimulating factors that act to regulate growth, differentiation, and activation of haematopoietic cells of multiple lineages. GM-CSF is produced by several airway cells including macrophages, eosinophils, T lymphocytes, fibroblasts, endothelial cells, airway smooth muscle cells, and epithelial cells.

Receptors

The GM-CSF receptor consists of a low affinity α chain with a second affinity converting β chain which is also shared by IL-3 and IL-5 receptors.[78 347] These receptors are usually distributed on granulocytes and monocytes, endothelial cells, and fibroblasts. Upregulation of the expression of α chain of GM-CSFR mRNA in macrophages in airway biopsy specimens of non-atopic asthma but not of atopic asthma has been reported.[348] Certain analogues of GM-CSF bind to the α chain of the receptor but not to the β chain complex without agonist effect, indicating that these mutants could act as antagonists of GM-CSF.[349]

Effects

GM-CSF is a pleiotropic cytokine that can stimulate the proliferation, maturation, and function of haematopoietic cells. It may be involved in priming inflammatory cells such as neutrophils and eosinophils and can prolong the survival of eosinophils in culture.[28 350] GM-CSF can enhance the release of superoxide anions and cys-LTs from eosinophils[351] and can also induce the synthesis and release of a number of cytokines including IL-1 and TNF-α from monocytes. GM-CSF induces non-haematopoietic cells such as endothelial cells to migrate and proliferate.[352]

Role in asthma

There is increased expression of GM-CSF in the epithelium of bronchial biopsy specimens from asthmatic patients[353] and in T lymphocytes and eosinophils after endobronchial challenge with allergen.[13 354] Increased circulating concentrations have been detected in patients with acute severe asthma,[355] and peripheral blood monocytes from asthmatic patients secrete increased amounts.[356] GM-CSF accounts for the increased eosinophil survival activity of BAL fluid.[31] It is the major LTC4 enhancing activity for eosinophils in the supernatant of cultured asthmatic alveolar macrophages.[357] Media obtained from cultured bronchial epithelial cells of asthmatic subjects increases the viability, superoxide production, and LTC4 production by eosinophils in vitro,[358] an effect abolished by a neutralising antibody to GM-CSF. Transient expression of the GM-CSF gene to the epithelium of rats using an adenoviral vector led to an accumulation of eosinophils and macrophages associated with irreversible fibrosis.[359] This indicates that GM-CSF may be involved in the chronic eosinophilia and airways remodelling of asthma.

STEM CELL FACTOR (SCF)

Synthesis and release

SCF (*c-kit* ligand) is produced by bone marrow stromal cells, fibroblasts (including bronchial subepithelial myofibroblasts and nasal polyp fibroblasts), and epithelial cells such as nasal polyp epithelial cells.[360–362]

Receptors

The receptor for SCF is *c-kit*, a receptor protein kinase, and is expressed on early haematopoietic progenitors and allows a synergistic response to SCF and lineage committing growth factors such as GM-CSF for myelocytes. *c-kit* expression decreases with cell maturation and is absent on mature cells released from bone marrow. However, *c-kit* expression increases on mast cells as they mature and are abundantly expressed on the surface of mast cells. *c-kit* is also expressed on human eosinophils.[363]

Effects

SCF acts as a survival factor for the early haematopoietic progenitor cells and synergises with other growth factors to regulate the proliferation and differentiation of cells. It is a major growth factor for human mast cells.[364 365] Two alternative spliced variants account for the different forms of SCF: a primarily membrane bound and the other primarily soluble after being released from the cell surface by proteolysis.[366] CD34+ bone marrow cells cultured in vitro with rh-SCF and IL-3 induces the development of mast cells and other haematopoietic lineages.[367]

Membrane bound SCF may influence mast cell adhesion[368] and soluble SCF is chemotactic for mast cells.[369] Removal of mast cells from either soluble or membrane bound SCF causes mast cells to undergo apoptosis.[370 371] SCF has modest direct activating capacity on the mast cell but is usually more active in priming mast cell responses to other stimuli such as IgE stimulated mediator release.[372–374] It causes the release of small amounts of IL-4 and TNF-α from human lung mast cells.[375] SCF stimulates VLA-4 mediated cell adhesion to fibronectin and VCAM-1 adhesion molecules on human eosinophils.[363]

Role in asthma

There is little information on the expression of SCF in asthmatic airways. It is expressed in the epithelium of nasal polyps from patients with allergic rhinitis.

Inhibitory cytokines

INTERLEUKIN 10

Synthesis and release

IL-10, previously known as cytokine synthesis inhibitor factor (CSIF), was originally identified as a product of murine T helper (Th2) clones that suppressed the production of cytokines by Th1 clones responding to stimulation of antigen.[376] In humans Th0, Th1, and Th2-like CD4+ T cell clones, cytotoxic T cells, activated monocytes and peripheral blood T cells including CD4+ and CD8+ T cells have the capacity to produce IL-10.[377] [378] Mast cells also have the capacity to produce IL-10. Constitutive IL-10 secretion occurs in the healthy lung with the major source being the alveolar macrophage; however, the circulating monocyte elaborates more IL-10 than the alveolar macrophage.[379]

Receptors

IL-10R is a member of the class II subgroup of cytokine receptors, the IFN-receptor family. IL-10R has been characterised and cloned from a human lymphoma cell line[380] and is expressed in several lymphoid and myeloid cells[381] and also on NK cells.[382] IL-10R is highly effective in recruiting the signalling pathways of IL-6 type cytokine receptors including STAT1 and STAT3.[383] The inhibitory effect of IL-10 on monocytes appears to be dependent on NF-κB.[384] The specific signalling pathway of IL-10R has not yet been definitely characterised.

Effects

IL-10 is a pleiotropic cytokine that can exert either immunosuppressive or immunostimulatory effects on a variety of cell types. It is a potent inhibitor of monocyte/macrophage function, suppressing the production of a number of pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, MIP-1α, and IL-8[385–387] although the release of MCP-1 is increased.[387] IL-10 inhibits monocyte MHC class II, B7.1/B7.2 and CD23 expression and accessory cell function. Accessory signals mediated by B7 molecules through CD28 on the surface of T cells are essential for T cell activation. Expression of IL-10 by antigen presenting cells may be an established pathway for the induction of antigen specific tolerance such as that to allergens.[388] By contrast, IL-10 upregulates the monocyte expression of IL-1ra, another anti-inflammatory cytokine.[389] IL-10 suppresses the synthesis of superoxide anions and NO by activated monocytes/macrophages.[390] An IL-10 antibody enhances the release of cytokines from activated monocytes, suggesting that this cytokine may play an inhibitory role when the cell is stimulated.[386] IL-10 inhibits the stimulated release of RANTES and IL-8 from human airway smooth muscle cells in culture.[116] [117] It inhibits the production of IFN-γ and IL-2 by Th1 lymphocytes[376] and IL-4 and IL-5 production by Th2 cells by interfering with B7-CD28 dependent signals.[391] [392] IL-10 also inhibits eosinophil survival and IL-4 induced IgE synthesis. On the other hand, IL-10 acts on B cells to enhance their viability, cell proliferation, immunoglobulin secretion with the isotype switch and class II MHC expression. It decreases IL-4 induced IgE switch in peripheral blood mononuclear cells but potentiates IgE production in B cells that are already switched to produce IgE.[393] IL-10 is also a growth co-stimulator for thymocytes and mast cells,[394] as well as an enhancer of cytotoxic T cell development.[395] It also activates the transcription of genes for mast cell derived proteases and enhances the production of the tissue inhibitor of metalloproteinases of monocytes and tissue macrophages while decreasing metalloproteinase biosynthesis.[396]

Role in asthma

There is significantly less IL-10 mRNA and protein expressed in alveolar macrophages of asthmatic subjects than in those from non-asthmatic individuals.[25] [397] Triggering of CD23 molecule by anti-CD23 monoclonal antibodies induces IL-10 production by human monocytes.[398] An IL-10 polymorphism on the transcription initiation site could be responsible for reduced IL-10 release.[397] Another polymorphism upstream from this site was associated with increased total serum IgE.[399] Inhaled corticosteroid treatment restores the reduced IL-10 release from macrophages of asthmatic subjects[25] and theophylline increases IL-10 secretion.[400] On the other hand, other studies indicate that there are increased numbers of macrophages and T cells expressing IL-10 mRNA in the BAL fluid of patients with asthma.[401]

IL-10 inhibits the late response and the influx of eosinophils and lymphocytes after allergen challenge in the Brown-Norway rat.[402] Co-instillation of IL-10 by the intranasal route significantly inhibits the peritoneal and lung eosinophilia induced by ovalbumin in immunised mice.[403] [404] Given its anti-inflammatory properties and these effects in animal models of allergic inflammation, IL-10 may have beneficial effects in asthma.[405] However, no such studies have been performed yet. Administration of IL-10 to normal volunteers induced a fall in circulating CD2, CD3, CD4, and CD8 lymphocytes with suppression of mitogen induced T cell proliferation and reduction of TNF-α and IL-1β production from whole blood stimulated with endotoxin ex vivo.[406]

INTERLEUKIN 1 RECEPTOR ANTAGONIST (IL-1RA)

IL-1ra has been isolated from supernatants of monocytes cultured on aggregated immunoglobulin or with immune complexes,[407] [408] alveolar macrophages,[409] and urine of patients with fever or myelomonocytic leukaemia.[410–412] IL-1ra shares 26% and 19% amino acid homology with IL-1α and IL-1β, respectively. It binds to the IL-1 receptor with a similar affinity to IL-1α or IL-1β[413] and inhibits most effects of IL-1 on cells, such as thymocyte proliferation, IL-2 synthesis by T cells, and PGE$_2$ and collagenase production by fibroblasts.[413–416] IL1-ra is preferentially produced by alveolar macrophages compared with monocytes,[417] which may underlie the diminished IL-1

bioactivity produced by alveolar macrophages compared with monocytes.[253 417 418] Other IL-1 receptor inhibitors have been described.[419 420]

IL-1ra blocks proliferation of Th2 but not Th1 clones in vitro.[421] Increased expression of IL-1β and IL-1ra in asthmatic airway epithelium has been reported.[295] After treatment with inhaled corticosteroids the expression of IL-1β is reduced but IL-1ra is unchanged, thus tipping the balance away from inflammation.[296] In a human airway epithelial cell line corticosteroids increase the expression of IL-1ra.[422] In an ovalbumin sensitised guinea pig model an aerosol of IL-1ra given immediately before allergen challenge resulted in protection against bronchial hyperresponsiveness and accumulation of pulmonary eosinophils.[423] In a similar model the late phase response with the number of hypodense eosinophils in BAL fluid was inhibited.[424] Trials of IL-1ra in asthma are underway.

INTERFERON γ

Synthesis and release
IFN-γ was originally identified as a product of mitogen stimulated T lymphocytes that inhibited viral replication in fibroblasts. The only known sources of IFN are CD4+ and CD8+ T cells and NK cells.

Receptors
IFN-γ receptor is a single transmembrane protein, a member of the cytokine receptor type II superfamily. Although the receptor binds IFN-γ with high affinity, signal transduction requires a species-specific accessory protein that associates with the extracellular domain of the receptor. The receptor is expressed on T cells, B cells, monocytes/macrophages, dendritic cells, granulocytes, and platelets. Epithelial and endothelial cells also express these receptors.

Effects
IFN-γ has extensive and diverse immunoregulatory effects on various cells. It is produced by Th1 cells and exerts an inhibitory effect on Th2 cells.[425] IFN-γ inhibits antigen induced eosinophil recruitment in the mouse.[426] However, it may also have pro-inflammatory effects and may activate airway epithelial cells to release cytokines and express adhesion molecules.[427] IFN-γ has an amplifying effect on the release of TNF-α from alveolar macrophages induced by IgE triggering or by endotoxin[323 428] and increases the expression of class I and class II MHC molecules on macrophages and epithelial cells. IFN-γ is a powerful and relatively specific inhibitor of IL-4 induced IgE and IgG$_4$ synthesis by B cells.

IFN-γ increases the production of IL-1, PAF, and H$_2$O$_2$ from monocytes, in addition to downregulating IL-8 mRNA expression that is upregulated by IL-2.[429–431] IFN-γ also synergises the effects of TNF-α in the production of RANTES from airway smooth muscle cells.[116] On the other hand, it inhibits IL-10 production from monocytes,[432] which in turn leads to an upregulation of TNF-α transcription.[433] Thus, IFN-γ promotes cell mediated cytotoxic responses while inhibiting allergic inflammation and IgE synthesis.

IFN-γ upregulates class II molecules on monocytes/macrophages and dendritic cells and induces de novo expression on epithelial, endothelial and other cells, thus making them capable of antigen presentation.

Role in asthma
There is reduced production of IFN-γ by T cells of asthmatic patients and this correlates with disease severity.[434 435] No polymorphisms of the IFN-γ gene have been associated with asthma.[436] Administration of exogenous IFN-γ prevents the airway eosinophilia and hyperresponsiveness following allergen exposure in mice.[437 438] Liposome mediated gene transfer of IFN-γ to the pulmonary epithelium in sensitised mice before secondary antigen exposure also inhibited the pulmonary allergic response.[439] IFN-γ receptor knock out mice develop a prolonged airway eosinophilia in response to allergen.[440] IFN-γ inhibits allergic eosinophilia[437 441] and airway hyperresponsiveness, probably by inducing the formation of IL-10. These studies indicate that IFN-γ has a potential modulating effect on allergen responses. Allergen immunotherapy of asthmatic patients results in increased production of IFN-γ by circulating T cells[442] and in an increase in IFN-γ producing T cells in nasal biopsy specimens.[443] Corticosteroid treatment also increases IFN-γ expression in asthmatic airways,[444] but in corticosteroid resistant patients IFN-γ is unexpectedly reduced.[71] In asthmatic patients nebulised IFN-γ reduces the number of eosinophils in BAL fluid, indicating its therapeutic potential in asthma.[445]

INTERLEUKIN 12

Synthesis and release
IL-12 was initially recognised as a cytokine capable of synergising with IL-2 to increase cytotoxic T lymphocyte responses, and also as an inducer of IFN-γ synthesis by resting human peripheral blood mononuclear cells in vitro. IL-12 is secreted by antigen presenting cells including B lymphocytes, monocytes/macrophages, and dendritic cells.[446 447]

Receptors
IL-12 receptors are expressed on T cells and NK cells. One component of the IL-12 receptor complex is related to gp130.[448]

Effects
IL-12 enhances the growth of activated T cells and NK cells[449–452] and enhances cytotoxic T cell and NK activity.[449 453 454] IL-12 stimulates NK cells and T cells to produce IFN-γ,[453 455–457] promotes in vitro differentiation of mouse and human T cells that secrete IFN-γ and TNF-α,[451 455 458 459] and inhibits the differentiation of T cells into IL-4 secreting cells.[458 459] IL-12 indirectly inhibits IL-4 induced human IgE responses by IFN-γ dependent and independent mechanisms in vitro.[460] Thus, IL-12 can primarily regulate Th1 cell differentiation while suppressing the expansion of Th2 cell clones[458] by early priming of undifferenti-

ated Th cells for IFN-γ secretion.[461] Thus, IL-12 may play an important role in directing the development of Th1-like T cell responses against intracellular pathogens whilst inhibiting the development of Th2-like responses and IgE synthesis. IL-12 may play an important role in inhibiting inappropriate IgE synthesis and allergic inflammation as a result of allergen exposure.

Role in asthma

IL-12 may play an important part in inhibiting inappropriate IgE synthesis and allergic inflammation as a result of allergen exposure. Treatment of mice with IL-12 during active sensitisation reduced antigen induced influx of eosinophils in BAL fluid, inhibited IgE synthesis, and abolished antigen induced bronchial hyperresponsiveness.[462] Once an inflammatory response is established there is an inhibition of antigen induced bronchial hyperresponsiveness and inflammation.[463] These effects of IL-12 are largely mediated by IFN-γ.[464] In mice IL-12 administered at the time of allergic sensitisation decreased specific IgE, tracheal ring responsiveness to acetylcholine, and eosinophilia in BAL fluid after allergen challenge, together with IL-5 and IL-10 downregulation; IL-12 administered after sensitisation did not alter specific IgE levels, had little effect on tracheal ring responsiveness, and a modest effect on the recruitment of eosinophils, together with IL-5 downregulation but IL-12 upregulation.[465] Thus, the effect of IL-12 is dependent on the timing of its administration in relation to active sensitisation.

The production of IL-12 and IL-12 induced IFN-γ release is reduced in whole blood cultures from patients with allergic asthma compared with normal subjects.[466] There is a reduction of IL-12 mRNA expression in airway biopsy specimens of patients with allergic asthma compared with normal subjects but, following treatment with oral corticosteroids, the levels of IL-12 mRNA increased in patients with corticosteroid sensitive asthma while no significant changes were observed in those with corticosteroid resistant asthma.[206] This contrasts with the inhibitory effects of corticosteroids on IL-12 production in human monocytes in vitro.[88] Allergen immunotherapy results in an increase in IL-12 expression.[467] PGE_2, $β_2$ agonists, and corticosteroids inhibit IL-12 production from monocytes.[88 468 469]

Chemokines

Chemokines are chemotactic cytokines of 8–10 kDa involved in attracting leucocytes into tissues. Over 40 chemokines have now been recognised[470] and they are divided into families according to their structure. The two major groups are CC chemokines (β chemokines) in which two cysteine residues are adjacent to each other and CXC chemokines (α chemokines) in which these residues are separated by another amino acid. The CC chemokines are involved in chemoattraction of eosinophils, monocytes, and T lymphocytes and are therefore of greatest relevance to asthma.

CC CHEMOKINES

Synthesis and release

Macrophage inflammatory protein 1α (MIP-1α) and MIP-1β were purified from culture media of endotoxin stimulated mouse macrophages[471] and their genes can be coordinately expressed after stimulation of T cells (for example, with anti-CD3), B cells, or monocytes and macrophages (for example, with lipopolysaccharide).[472–476] MIP-1α gene is rapidly induced in human monocytes following adherence to endothelial cells and to other substrates.[477] Monocyte chemoattractant protein 1 (MCP-1) is a monocyte chemoattractant and activating factor and is the best characterised CC chemokine, having been purified and cloned from different sources.[478–480] The other CC chemokines—I-309, RANTES, and HC-14—were purified and cloned as products of activated T cells.[474 481 482] Substractive hybridisation was used to find genes expressed uniquely in T cells and this led to the discovery of RANTES (Regulated on Activation, Normal T cell Expressed, and Secreted) cDNA encoding a polypeptide of 91 amino acids with an 8 kDa secreted protein. RANTES gene is expressed in IL-2 dependent T cell lines. In peripheral blood mononuclear cells low but detectable levels of RANTES transcripts can be measured in unstimulated cells and an increase in mRNA 5–7 days after antigen or stimulation with phytohaemagglutinin.[481] HC-14, discovered from IFN-γ stimulated monocytes, now called MCP-2, has also been isolated from osteosarcoma cell cultures,[483] which also yielded MCP-3 which has been cloned and expressed.[484 485] MCP-4 has also been identified within a large scale sequencing and expression programme for the discovery of new chemokines.[486 487] Eotaxin is a chemokine selective for eosinophils which was discovered in BAL fluid obtained from an experimental model of allergen exposure of sensitised guinea pigs[488] and subsequently shown to be present in humans.[489] Another functionally similar chemokine, eotaxin-2, has recently been described.[30] STCP-1 is another new CC chemokine which is a chemoattractant for Th2 cells.[490]

In general, monocytes and tissue macrophages are a rich source of CC chemokines, usually associated with de novo synthesis. MCP-1 with MCP-2 is a major stimulated product of monocytes. Lymphocytes are sources of some CC chemokines, particularly RANTES,[474 481 491] I-309,[474 492] MIP-1α,[473 474 491] and MIP-1β.[473 493] Neutrophils can produce MIP-1α.[494] Eosinophils of patients with hypereosinophilic syndrome express mRNA for MIP-1α.[302] Epithelial cells stimulated with IL-1β or TNF-α produce RANTES,[311] MCP-4,[495] and eotaxin[496] but not MIP-1α. MCP-1, RANTES, and eotaxin immunoreactivity is present in human airway epithelium.[311 497] RANTES and eotaxin are produced by cultured human airway smooth muscle cells,[116] and MCP-1 and RANTES by human eosinophils.[498 499]

Receptors

The chemokine receptors form a family of structurally and functionally related proteins, being members of the superfamily of heptahelical, rhodopsin-like, G protein coupled receptors. At least 10 CC chemokine receptors have been identified. These include CCR1 which binds MIP-1α, RANTES and MCP-3,[500 501] CCR2 which binds MCP-1 and MCP-3,[502 503] CCR3 which binds eotaxin, RANTES, MCP-3, and MCP-4,[504] CCR4 which binds MCP-1, MIP-1α, and RANTES,[505 506] and CCR5 which binds MIP-1α, MIP-1β, and RANTES.[507] CCR6 is a specific receptor for a new lymphocyte directed CC chemokine called liver and activation regulated chemokine (LARC or MIP-3α),[508] CCR7 is a receptor for another novel CC chemokine, EBI1 ligand chemokine (ELC or MIP-3β),[509] and CCR8 is a specific receptor for the chemokine I309.[510]

Chemokine receptor usage by eosinophils has generated considerable interest because of the possibility of using receptor antagonists to block eosinophil influx and degranulation in asthma. CCR3 is considered to be the eotaxin receptor mediating mainly chemotaxis and has been identified as being the major CC chemokine receptor on eosinophils and basophils. An increase in CCR3 expression is observed in bronchial biopsy specimens obtained from asthmatic subjects[511]. A monoclonal antibody selective for CCR3 inhibits eosinophilia.[512] Basophils also express CCR3 which mediate chemotaxis. However, the release responses of basophils are mediated by activation of the MCP-1 receptor (CCR2) expressed on basophils but not on eosinophils. Eosinophils also express CCR1, which is responsible for the MIP-1α and partly for the RANTES response. CCR5 is not expressed on eosinophils or basophils, but on monocytes which also express CCR1, CCR2, and CCR4. Several cytokines including IL-2, IL-4, IL-10, and IL-12 can upregulate CCR1 and CCR2 receptors in CD45RO+ blood lymphocytes associated with an increase in chemotactic activity of RANTES and MCP-1 on these cells.[513] Differential chemokine receptor usage on different types of T helper cells is now also recognised. Th2 cells preferentially express CCR4 and CCR3[514 515] while Th1 cells express CCR5.[514 516]

Effects

Chemokines may play a major part in activating migrating leucocytes and endothelial cells to increase adhesiveness and in establishing a chemotactic gradient. MIP-1α immobilised by binding to proteoglycans binds to endothelium to trigger adhesion of T cells, particularly CD8+ T cells to VCAM-1.[517] It has been localised to lymph node endothelium and could act as a tethered ligand on endothelial cells and could therefore provide the required signals for activation of lymphocyte integrins for adhesion to endothelium and migration.

RANTES is a powerful eosinophil chemoattractant, being as effective as C5a and 2–3 times more potent than MIP-1α.[518 519] RANTES upregulated the expression of CD11b/CD18 on eosinophils.[520] RANTES and MIP-1α induce exocytosis of eosinophil cationic protein from cytochalasin B treated cells, although RANTES is relatively weak in this effect.[518] When injected into the skin of dogs RANTES induced an infiltration of eosinophils and monocytes.[521] RANTES, but not MIP-1α, also elicited a respiratory burst from eosinophils.[518] MCP-2, MCP-3, and MCP-4 are potent chemoattractants for eosinophils.[486 522–524] Eotaxin and eotaxin-2 have selective chemoattractant activities for eosinophils in vitro and in vivo in the skin.[30] Eotaxin also induces α₄ and β₁ integrin expression on eosinophils.[525 526] Cooperation between IL-5 and CC chemokines such as RANTES and eotaxin is increasingly recognised with IL-5 being essential for mobilising eosinophils from the bone marrow during allergic reactions and for local release of chemokines to induce homing and migration into tissues.[32 152 165] Eotaxin also induces release of eosinophils and their progenitors from the bone marrow.[33]

RANTES is also a chemoattractant for memory T cells in vitro.[527] Human MIP-1α and MIP-1β are chemoattractants for distinct subpopulations of lymphocytes with MIP-1α towards CD8+ and MIP-1β towards CD4+ T lymphocytes.[528] RANTES attracts both phenotypes and acts on resting and activated T lymphocytes, while MIP-1α and MIP-1β are effective on anti-CD3 stimulated cells only.[529] On the other hand, MIP-1β but not MIP-1α is chemotactic for resting T cells and enhances the adherence of CD8+ but not CD4+ cells to VCAM-1.[530] MCP-1, MCP-2, MCP-3, and MCP-4 induce T cell migration.[531 532] NK cells migrate vigorously in response to RANTES, MIP-1α, and MCP-1.[533 534] Human recombinant IP-10 is a chemoattractant for human monocytes and promotes T cell adhesion to endothelial cells.[535] The C chemokine lymphotactin also shares T lymphocyte chemoattractant activity.[536]

CC chemokines are powerful stimulants of basophils. MCP-1 is as potent as C5a in stimulating exocytosis in human basophils,[537–539] with release of high levels of histamine. In the presence of IL-3, IL-5, or GM-CSF there is enhanced release of histamine and production of LTC4.[537 539] RANTES and MIP-1α are less effective releasers of histamine from basophils. MIP-1α is inactive on basophils.[540] RANTES is the most effective basophil chemoattractant,[538 540 541] while MCP-1 is more effective as an inducer of histamine and leukotriene release.[540] Eotaxin-1 and eotaxin-2 also are chemoattractant for basophils, in addition to stimulating the release of histamine and LTC4.[30]

CC chemokines MCP-1, RANTES, I-309, MCP-2, and MCP-3 attract monocytes in vitro,[483 527 542–546] and MCP-1, MCP-2, and MCP-3 induce a selective infiltration of monocytes in animal skin.[483 547] All CC chemokines stimulate $[Ca^{++}]_i$ release.[540 546] MCP-1 also induces a respiratory burst, an expression of β₂ integrins (CD11b/CD18 and CD11c/CD18), and the production of IL-1 and IL-6.[544 547 548]

Dendritic cells increased intracellular calcium release and migrated in response to MCP-3, MCP-4, MIP-1α, and MIP-5.[549]

Role in asthma

The potential role of chemokines in asthma is supported by observations that many cell types present in the asthmatic airway have the potential of generating chemokines, in particular monocytes/macrophages, T cells, airway smooth muscle cells, and airway epithelium. Increased levels of MCP-1, RANTES, and MIP-1α have been reported in BAL fluid from asthmatic subjects, and the eosinophil chemoattractant activity of BAL fluid of asthmatic subjects was blocked by antibodies to RANTES, MCP-3, and IL-5.[155 550] The increased levels of MCP-1 and RANTES were not confirmed in other studies[551 552]; eotaxin and RANTES may preferentially bind to components of sputum. Levels of MIP-1α, MCP-1, and RANTES were raised in BAL fluid following segmental allergen challenge.[12 552] RANTES but not MIP-1α mRNA expression has been shown to be increased in bronchial biopsy specimens from patients with mild asthma.[553] Epithelial cells, but not endothelial cells, preferentially secrete RANTES through the apical cell surface in asthma, thereby establishing a chemical gradient for chemotaxis across the epithelium.[554] No differences in MIP-1α mRNA expression were observed in alveolar macrophages obtained from normal and asthmatic subjects but MIP-1α release is increased from alveolar macrophages of asthmatic patients.[25] Increased expression of RANTES and MCP-3 mRNA has been reported in the airway submucosa of patients with allergic and non-allergic asthma.[555] Although RANTES immunostaining is present in the airway epithelium with no differences between normal and asthmatic subjects,[553] MCP-1 is overexpressed in asthmatic epithelium.[497] Increased plasma levels of RANTES are present during asthma exacerbations.[556] Eotaxin mRNA and protein expression is increased in the airways of asthmatics, mainly in epithelium, T cells, macrophages, and eosinophils.[511 557 558] In the guinea pig allergen challenge induces eotaxin expression, mainly in airway epithelium and macrophages.[559] Increased expression and release of eotaxin occurs after allergen challenge in asthmatic subjects.[560]

Targeted disruption of eotaxin partially reduces antigen induced tissue eosinophilia in the mouse.[156] An anti-MCP-3 antibody inhibits allergen induced eosinophilic inflammation in the mouse.[561] Met-RANTES is an antagonist of eosinophil functions following stimulation with RANTES, MCP-3, and eotaxin, antagonising effects mediated through CCR1 rather than CCR3.[562] The availability of specific CC chemokine receptor antagonists, particularly of the CCR3 receptor, will make it possible to examine the contribution of these chemokines in allergic inflammation and asthma.

CXC CHEMOKINES

Synthesis and release

IL-8 (also referred to as neutrophil activating protein 1, NAP-1) has major actions as a neutrophil chemoattractant and activator. Other CXC chemokines similar to IL-8 include neutrophil activating protein 2 (NAP-2)[563] arising from N-terminal processing of platelet basic protein, GRO-α, GRO-β, and GRO-γ,[564 565] epithelial cell derived neutrophil activating protein (ENA-78),[566] and granulocyte chemotactic protein 2 (GCP-2).[567] A secreted protein produced by lipopolysaccharide stimulated murine macrophages called macrophage inflammatory protein 2 (MIP-2) is a chemoattractant for human neutrophils and is closely related to GRO.[568] In general, monocytes and tissue macrophages are a rich source of CXC chemokines, usually associated with de novo synthesis. Monocytes respond to a large variety of pro-inflammatory agents including IL-1β, TNF, GM-CSF, IL-3, lipopolysaccharide, immune complexes to release IL-8. IL-8 has also been induced following adherence of monocytes to plastic and by changes in ambient oxygen.[569 570] Eosinophils also release IL-8 after stimulation with calcium ionophore A23187, but not with TNF-α or IL-1β.[571] Airway epithelial cells and airway smooth muscle cells stimulated with IL-1β or TNF-α produce IL-8.[117 572–575] IL-8 expression by epithelial cells is increased by respiratory syncytial virus infections[576] and on exposure to neutrophil elastase.[577]

Several transcriptional regulatory elements can bind to the region preceding the first exon including NF-κB, NF-IL-6, AP-1, glucocorticoid element, and an octamer binding motif.[578] NF-IL-6 and NF-κB-like factors may act as *cis*-acting elements in IL-8 mRNA expression.[579] IL-8 mRNA expression after stimulation with IL-1β or TNF-α is rapid and results, at least partly, from transcriptional activation as shown by nuclear run-on assays.[575 580–582] A secondary phase of IL-8 mRNA expression following an early rapid increase induced by IL-1 is observed with cultured human airway epithelial cells.

Receptors

At least four CXC receptors have been identified. For IL-8 there are high affinity (CXCR1) and low affinity (CXCR2) receptors which are mainly expressed on neutrophils.[583 584] CXCR3 is the receptor for IP-10, MIG, and I-TAC and is found mainly on activated T cells, particularly Th1 cells and natural killer cells,[585 586] while CXCR4 is the receptor for SDF-1 and is localised to dendritic cells.[549] These receptors are a family of structurally and functionally related proteins, being members of the superfamily of heptahelical, rhodopsin-like, G protein coupled receptors. IL-8 on neutrophils also induces G protein activation.[587] CXCR1 is specific for IL-8 and other CXC chemokines do not bind to it.[583] Its sequence is 77% identical to that of CXCR2.[583] CXCR2 can be activated by CXC chemokines containing the sequence Glu-Leu-Arg in the N-terminal

domain, including IL-8, GRO, and NAP-2, but not by CC chemokines.[584 588]

Effects
IL-8 is a mainly neutrophil chemoattractant and activator which induces shape change, a transient rise in $[Ca^{++}]_i$, exocytosis with release of enzymes and proteins from intracellular storage organelles, and respiratory burst through activation of NADPH oxidase.[589] It also upregulates the expression of two integrins (CD11b/CD18 and CD11c/CD18) during exocytosis of specific granules.[590 591] IL-8 activates neutrophil 5-lipoxygenase with the formation of LTB4 and 5-HETE,[592] and also induces the production of PAF.[593]

IL-8 can also induce an increase in $[Ca^{++}]_i$, shape change, and release of eosinophil peroxidase from the eosinophils of patients with hypereosinophilic syndrome.[594] It has a small amount of chemotactic activity for both CD4+ and CD8+ T lymphocytes[595] but intradermal injection of IL-8 in humans does not attract lymphocytes.[596 597] IL-8 induces the release of histamine[598 599] and cys-LTs[598] from human blood basophils with enhanced release with IL-3, IL-5, or GM-CSF pretreatment.[600] It induces release of a small amount of $[Ca^{++}]_i$ and respiratory burst.[601]

Role in asthma
Enhanced co-expression of IL-8 and GM-CSF in bronchial epithelial cells of patients with asthma has been reported.[602] Free IL-8 has been detected in the serum and bronchial tissue of subjects with severe atopic asthma but not in normal subjects or those with mild atopic asthma, suggesting that IL-8 may be a marker of severe asthma. IL-8 was also found to be complexed with IgA, levels of which were raised in bronchial tissue in asthma.[603] However, in segmental local challenge studies of patients with allergic asthma IL-8 increased levels correlated with neutrophil influx,[604] indicating that IL-8 may be responsible for neutrophil chemotaxis. Enhanced release of IL-8 has been demonstrated from alveolar macrophages obtained from patients with mild asthma compared with those from normal subjects.[605] In patients with mild asthma there is no increase in IL-8 levels in induced sputum, in contrast to the markedly raised levels in patients with COPD and bronchiectasis.[606 607] Increased levels of IL-8 have been measured in the BAL fluid of patients with asthma and bronchitis.[607]

IL-8 possesses chemotactic activity for primed eosinophils.[608] Human IL-8 is able to induce accumulation of eosinophils in guinea pig skin[609] and an anti-IL-8 antibody inhibited IL-1 induced eosinophil accumulation in rat skin.[298] Local instillation of rh-IL-8 to the nose caused an extravascular accumulation of eosinophils in the nasal mucosa of atopic but not in normal subjects.[610]

Growth factors
PLATELET-DERIVED GROWTH FACTOR (PDGF)
Synthesis and release
PDGF is released from many different cells in the airways and consists of two peptide chains so that AA, BB, or AB dimers may be secreted by different cells. Both PDGF-A and PDGF-B chains are synthesised as high molecular mass precursors which are then extensively processed before secretion.[611 612] Post-translational glycosylation and proteolytic cleavage[611 613 614] both contribute to the heterogeneity of the apparent molecular mass of mature proteins. Most of the PDGF present in human platelets (from which PDGF was originally isolated) has been identified as AB dimer, although BB and AA dimers also exist.[615 616] PDGF-like activity in the conditioned media of various cells such as those derived from smooth muscle consists predominantly of the AA dimer.[617] The sources of PDGF include platelets, macrophages, endothelial cells, fibroblasts, airway epithelial cells, and vascular smooth muscle cells. Various stimuli such as IFN-γ on alveolar macrophages, hypoxia, basic FGF, mechanical stress on endothelial cells, serum, TNF-α, IL-1, and TGF-β on fibroblasts can induce PDGF release.

Receptors
The PDGF receptors belong to a family of closely related receptor proteins that include the receptor for monocyte-colony stimulating factor and the *c*-kit receptor.[618] PDGF exerts its actions through a family of at least two classes of PDGF receptors, α and β.[619–621] They are single transmembrane glycoproteins with an intracellular tyrosine kinase domain.[622] Binding of PDGF dimers induces receptor dimerisation with three possible configurations (αα, αβ, ββ). The PDGF receptor α subunit binds both PDGF-A and -B chains, whereas the β receptor subunit binds only PDGF-B chains. Thus, PDGF-AA binds only to PDGF receptor αα dimers, PDGF-AB to receptor αα and αβ dimers, and PDGF-BB to all three configurations.[623 624] These receptors are widely distributed on cells of mesenchymal origin including fibroblasts and smooth muscle cells. Because of their critical role in cell growth, expression of PDGF receptors is usually tightly controlled. However, they can be regulated by TGF-β which can increase the expression of PDGF receptor α on human skin fibroblasts[625 626] or by basic fibroblast growth factor which induces the expression of PDGF α receptor on bronchial smooth muscle.[627]

Effects
PDGF is a major mitogen whose main regulatory role is directed at the cell cycle, acting as a competence factor triggering early events of the cell cycle leading to DNA synthesis and mitosis.[628] PDGF induces the expression of competence genes including the protooncognes *c-myc*, *c-fos*, and *c-jun*.[629 630] PDGF may activate fibroblasts to proliferate and secrete collagen[631] and may also stimulate proliferation of airway smooth muscle[48] which is mediated via the receptor.[632] PDGF is a chemoattractant for connective tissue cells[633 634] and can stimulate fibroblasts to contract collagen lattices.[635]

Role in asthma

Levels of PDGF-AA, -AB, and -BB are not raised in asthma and immunohistochemistry for PDGF-AA and -BB, and for PDGFR-α and PDGFR-β are not increased.[636] Expression of PDGF in the bronchial mucosa of asthmatic patients with thickened lamina reticularis is not increased compared with normal subjects.[637] Similar results were obtained in another study in which PDGF was immunolocalised to tissue macrophages.[638] One source of PDGF B-chain is the eosinophil in nasal polyps or bronchial biopsy specimens from patients with asthma.[639] This has raised the possibility that eosinophils, together with their ability to express TGF-β, are involved in airway remodelling in patients with asthma.

TRANSFORMING GROWTH FACTOR β (TGF-β)
Synthesis and release

Monocytes express TGF-β mRNA constitutively but only release the protein when activated.[640 641] Pulmonary macrophages may store large amounts of TGF-β during pulmonary inflammation.[642] Lung fibroblasts themselves may be a source of TGF-β,[643] but it is also secreted by inflammatory cells including eosinophils,[644 645] neutrophils,[646] and airway smooth muscle cells, and structural cells such as epithelial cells.[647] Mast cells may also be another source.[254] TGF-β is present in the epithelial lining fluid of the normal lower respiratory tract.[648] TGF-β mRNA and protein have been found to be abundantly expressed in human lung, with TGF-β_1 precursor being immunolocalised throughout the airway wall including the epithelium and in alveolar macrophages, and the mature protein localised mainly within the connective tissue of the airway wall.[649]

Receptors

TGF-β receptor exists in three forms: a high affinity type I and II, and a low affinity type III.[650] The high affinity receptors are serine/threonine kinases related to the activin receptor and are thought to associate to mediate signal transduction probably through serine/threonine phosphorylation. The type II receptor includes β-glycan and endoglin and does not transduce signals but may concentrate TGF-β on the cell surface and present the ligand to the other receptors.

Effects

TGF-β comprises a family of growth modulating cytokines with an important influence on the turnover of matrix proteins.[651] They may either inhibit or stimulate proliferation of fibroblasts depending on the presence of other cytokines. TGF-β induces the transcription of fibronectin which can function as a chemotactic agent and growth factor for human fibroblasts.[652 653] It may also be involved in the repair process of airway epithelial damage characteristic of asthma, since TGF-β is a potent inducer of differentiation for normal epithelial cells.[654] TGF-β is a potent profibrotic cytokine that stimulates fibroblasts to promote the synthesis and secretion of many proteins of the extracellular matrix.[655] It is also a potent chemoattractant for many cell types including monocytes, fibroblasts, and mast cells.[656 657] TGF-β activates monocytes to produce other cytokines such as TNF-α, TGF-α, TGF-β, PDGF-B, and IL-1. TGF-β has complex actions on the immune system. In general, TGF-β_1 inhibits both T and B cells. Thus, TGF-β inhibits IL-1 dependent lymphocyte proliferation[287] and blocks IL-2 mediated induction of IL-2 receptors on T cells.[658] TGF-β_1 can both decrease and increase airway smooth muscle proliferation.[659 660]

Role in asthma

Expression for both forms of TGF-β_1 is reported to be similar in lungs from normal and asthmatic subjects.[649] However, a greater number of airway mucosal eosinophils expressing TGFβ₁ mRNA and protein has been reported, correlating with the severity of asthma and the degree of subepithelial fibrosis.[661] This was not confirmed in other studies of asthmatic subjects in whom an increase in the lamina reticularis of the basement membrane was reported.[637 662] TGF-β_1 immunoreactivity has been observed in the epithelium and submucosal cells such as eosinophils and fibroblasts, with a greater expression in biopsy specimens from patients with chronic bronchitis than those with asthma.[663] Release of TGF-β_1 into the BAL fluid has been observed following segmental allergen challenge.[664] The possibility remains that TGF-β (together with PDGF) may be involved in the remodelling process of asthma, although it may also participate in modulating the T cell response.

FIBROBLAST GROWTH FACTOR (FGF)

FGF represents a family of heparin binding growth factors consisting of seven polypeptides including acidic (aFGF) and basic FGF (bFGF).[665] aFGF and bFGF are potent modulators of cell proliferation, motility, and differentiation. They are found associated with extracellular matrix. A major role has been proposed for FGF in the induction of angiogenesis.[666] bFGF induces an invasive phenotype in cultured endothelial cells, enabling them to penetrate the basement membrane in vitro.[667] It induces increased production of proteolytic enzymes, plasminogen activators, and collagenase.[667–669] bFGF binds to heparan sulphate proteoglycans in basement membranes in vivo.[670] In the human adult lung bFGF has been localised to vascular smooth muscle and in endothelial cells of blood vessels of the lungs.[671] It has also been detected in high levels in epithelial cells of the trachea and bronchi. bFGF increases the expression of PDGF-Rα in human airway smooth muscle and therefore indirectly stimulates proliferation.[627]

EPIDERMAL GROWTH FACTOR (EGF)

EGF and TGF-α, which do not bind heparin, also stimulate angiogenesis.[672] EGF expression is increased in the epithelium of bronchitic subjects and the submucosa of patients with

asthma.[663] It increases airway smooth muscle proliferation[49] and endothelin-1 potentiates EGF induced airway smooth muscle proliferation.[673] Since an increased number of blood vessels has been described in asthmatic airways,[9] these growth factors may be implicated. EGF expression is reported to be increased in the epithelium of patients with chronic bronchitis and in the submucosa of asthmatic patients.[663]

INSULIN-LIKE GROWTH FACTOR (IGF)

IGF is produced by airway epithelial cells.[674] It is a potent mitogen for airway smooth muscle proliferation[675] and appears to mediate the proliferative effect of LTD4 on airway smooth muscle proliferation.[676] IGF is a potent mitogen and activates MAP kinases in airway smooth muscle.[677] There is no difference in the expression of IGF in the airways submucosa of patients with asthma who have a thickened reticularis lamina of their basement membrane.[678] Inhaled corticosteroid treatment is associated with a reduction in the expression of IGF in the airways of patients with asthma, associated with a reduced lamina reticularis.[679]

Conclusion

The field of cytokine biology is moving very rapidly with the discovery of new molecules and of the basic mechanisms by which these cytokines act. Our review details the involvement of many cytokines in asthma and their contribution to the pathogenesis of asthma appears to be very diverse. Despite a large amount of information on the biological activities of cytokines and on their potential involvement in various aspects of asthmatic inflammation, much remains to be learnt about cytokines in day-to-day asthma. While current interest is focusing to a large extent on the immunoregulatory polarisation of T cells into Th2 cells as a cause of asthma, little is known about the stratification of the cytokines into the clinical stages of asthma. What are the profiles of the cytokine network at the "pre-asthma" stage prior to the onset of symptoms? When the clinical disease is established, do certain cytokines (or cytokine networks) become more prominent? In the presence of established airway wall remodelling, cytokines with proliferative activities on resident cells may be more important. This also raises the possibility that the severity of asthma may be related to differential cytokine expression.

An understanding of cytokine biology has led to the identification of several targets that could be developed as potential treatment for asthma.[680] Indeed, there is currently a large drive to test several inhibitors of cytokine effects in asthma, such as inhibitors of IL-5 which is a cytokine central to the development of tissue eosinophilic inflammation. Clinical studies of an antibody to IL-5 are currently underway. However, it is unclear to what extent blocking the effects of one single cytokine out of all the cytokines that are potentially involved will lead to important therapeutic effects. For example, in terms of eosinophilic inflammation, not only IL-5 but also the eosinophil selective chemokines may contribute. Testing such inhibitors will also address the question of, in this instance, the importance of eosinophils in causing clinical asthma, as distinct from the studies in animals. A study of the actions of these cytokines may provide other ways of blocking the effects of groups of cytokines. Corticosteroids may have beneficial effects in asthma by their ability to block the generation of several pro-inflammatory cytokines. Blocking the effects at an early stage of asthma may control or cause remission in the disease. Therefore, not only will greater understanding of asthma pathogenesis be achieved by studying cytokine biology, but also the potential for newer more effective treatments, perhaps even a cure.

1 Draper JC, Wietzerbin J. IFN-gamma decreases specific binding of tumor necrosis factor on murine macrophages. *J Immunol* 1991;**146**:1198–203.
2 Shepherd VL. Cytokine receptors in lung. *Am J Respir Cell Mol Biol* 1991;**5**:403–10.
3 Bousquet J, Chanez P, Lacoste JY, *et al*. Eosinophilic inflammation in asthma. *N Engl J Med* 1990;**323**:1033–9.
4 Djukanovic R, Wilson JW, Britten KM, *et al*. Quantitation of mast cells and eosinophils in the bronchial mucosa of symptomatic atopic asthmatics and healthy control subjects using immunohistochemistry. *Am Rev Respir Dis* 1990;**142**:863–71.
5 Azzawi M, Bradley B, Jeffery PK, *et al*. Identification of activated T lymphocytes and eosinophils in bronchial biopsies in stable atopic asthma. *Am Rev Respir Dis* 1990;**142**:1407–13.
6 Wenzel SE, Szefler SJ, Leung DYM, *et al*. Bronchoscopic evaluation of severe asthma: persistent inflammation associated with high dose glucocorticoids. *Am J Respir Crit Care Med* 1997;**156**:737–43.
7 Ebina M, Takahashi T, Chiba T, *et al*. Cellular hypertrophy and hyperplasia of airway smooth muscle underlying bronchial asthma. *Am Rev Respir Dis* 1993;**148**:720–6.
8 Roche WR, Beasley R, Williams JH, *et al*. Subepithelial fibrosis in the bronchi of asthmatics. *Lancet* 1989;i:520–4.
9 Li X, Wilson JW. Increased vascularity of the bronchial mucosa in mild asthma. *Am J Respir Crit Care Med* 1997;**156**:229–33.
10 Laitinen LA, Laitinen A, Haahtela T. Airway mucosal inflammation even in patients with newly diagnosed asthma. *Am Rev Respir Dis* 1993;**147**:697–704.
11 Robinson DS, Hamid Q, Ying S, *et al*. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. *N Engl J Med* 1992;**326**:298–304.
12 Holgate ST, Bodey KS, Janezic A, *et al*. Release of RANTES, MIP-1α, and MCP-1 into asthmatic airways following endobronchial allergen challenge. *Am J Respir Crit Care Med* 1997;**156**:1377–83.
13 Broide DH, Lotz M, Cuomo AJ, *et al*. Cytokines in symptomatic asthmatic airways. *J Allergy Clin Immunol* 1992;**89**:958–67.
14 Zhu Z, Tang W, Ray A, *et al*. Rhinovirus stimulation of interleukin-6 in vivo and in vitro: evidence for nuclear factor-κB-dependent transcriptional activation. *J Clin Invest* 1996;**97**:421–30.
15 Hamid Q, Azzawi M, Ying S, *et al*. Expression of mRNA for interleukins in mucosal bronchial biopsies from asthma. *J Clin Invest* 1991;**87**:1541–6.
16 Broide DH, Firestein GS. Endobronchial allergen challenge in asthma. Demonstration of cellular source of granulocyte-macrophage colony stimulating factor by in situ hybridization. *J Clin Invest* 1991;**88**:1048–53.
17 Robinson DS, Tsicopoulos A, Meng Q, *et al*. Increased interleukin-10 messenger RNA expression in atopic allergy and asthma. *Am J Respir Cell Mol Biol* 1996;**14**:113–7.
18 Lenschow DJ, Walunas TL, Bluestone JA. CD28/B7 system of T cell costimulation. *Annu Rev Immunol* 1996;**14**:233–58.
19 Geha RS. Regulation of IgE synthesis in humans. *J Allergy Clin Immunol* 1992;**90**:143–50.
20 Flint KC, Leung KBP, Hudspith BN, *et al*. Bronchoalveolar mast cells in extrinsic asthma: mechanism for the initiation of antigen specific bronchoconstriction. *BMJ* 1985;**291**:923–7.
21 Bradding P, Roberts JA, Britten KM, *et al*. Interleukin-4, -5 and -6 and tumor necrosis factor α in normal and asthmatic airways: evidence for the human mast cell as a source of these cytokines. *Am J Respir Cell Mol Biol* 1994;**10**:471–80.
22 Vercelli D, Jabara HH, Lee BW, *et al*. Human recombinant interleukin-4 induces FC4RII/CD23 on normal human monocytes. *J Exp Med* 1988;**167**:1406–16.
23 Viksman MY, Liu MC, Bickel CA, *et al*. Phenotypic analysis of alveolar macrophages and monocytes in allergic airway inflammation. I. Evidence for activation of alveolar macrophages, but not peripheral blood monocytes, in subjects with allergic rhinitis and asthma. *Am J Respir Crit Care Med* 1997;**155**:858–63.

24 Hallsworth MP, Soh CPC, Lane SJ, *et al*. Selective enhancement of GM-CSF, TNF-α, IL-1β and IL-8 production by monocytes and macrophages of asthmatic subjects. *Eur Respir J* 1994;**7**:1096–102.

25 John M, Lim S, Seybold J, *et al*. Inhaled corticosteroids increase interleukin-10 but reduce macrophage inflammatory protein-1 α, granulocyte-macrophage colony-stimulating factor and interferon-γ release from alveolar macrophages in asthma. *Am J Respir Crit Care Med* 1998;**157**:256–62.

26 Sanderson CJ, Warren DJ, Strath M. Identification of a lymphokine that stimulates eosinophil differentiation in vitro. Its relationship to interleukin 3, and functional properties of eosinophils produced in cultures. *J Exp Med* 1985;**162**:60–74.

27 Sanderson CJ. Interleukin-5, eosinophils and disease. *Blood* 1992;**79**:3101–9.

28 Hallsworth MP, Litchfield TM, Lee TH. Glucocorticosteroids inhibit granulocyte-macrophage colony-stimulating factor and interleukin-5 enhanced in vitro survival of human eosinophils. *Immunology* 1992;**75**:382–5.

29 Walker C, Virchow JC, Bruijnzeel PLB, *et al*. T cell subsets and their soluble products regulate eosinophilia in allergic and non allergic asthma. *J Immunol* 1991;**146**:1829–35.

30 Forssmann U, Uguccioni M, Loetscher P, *et al*. Eotaxin-2, a novel CC chemokine that is selective for the chemokine receptor CCR3, and acts like eotaxin on human eosinophil and basophil leukocytes. *J Exp Med* 1997;**185**:2171–6.

31 Park CS, Choi YS, Ki SY, *et al*. Granulocyte macrophage colony-stimulating factor is the main cytokine enhancing survival of eosinophils in asthmatic airways. *Eur Respir J* 1998;**12**:872–8.

32 Collins PD, Griffiths-Johnson DA, Jose PJ, *et al*. Co-operation between interleukin-5 and the chemokine, eotaxin, to induce eosinophil accumulation in vivo. *J Exp Med* 1995;**182**:1169–74.

33 Palframan RT, Collins PD, Severs NJ, *et al*. Mechanisms of acute eosinophil mobilization from the bone marrow stimulated by interleukin 5: the role of specific adhesion molecules and phosphatidylinositol 3-kinase. *J Exp Med* 1998;**188**:1621–32.

34 Rothenberg ME, Owen WFJ, Siberstein DS. Human eosinophils have prolonged survival, enhanced functional properties and become hypodense when exposed to human interleukin 3. *J Clin Invest* 1988;**81**:1986–92.

35 Owen WF, Rothenberg ME, Silberstein DS, *et al*. Regulation of human eosinophil viability, density and function by granulocyte/macrophage colony-stimulating factor in the presence of 3T3 fibroblasts. *J Exp Med* 1987;**166**:129–41.

36 Motojima S, Frigas E, Loegering DA, *et al*. Toxicity of eosinophil cationic proteins for guinea pig tracheal epithelium in vitro. *Am Rev Respir Dis* 1989;**139**:801–5.

37 Silberstien DS, Owen WF, Gasson JC. Enhancement of human eosinophil cytotoxicity and leukotriene synthesis by biosynthetic recombinant granulocyte-macrophage colony-stimulating factor. *J Immunol* 1986;**137**:3290–4.

38 Owen WF, Petersen J, Austen KF. Eosinophils altered phenotypically and primed by culture with granulocyte/macrophage colony-stimulating factor and 3T3 fibroblasts generate leukotriene C4 in response to FMLP. *J Clin Invest* 1991;**87**:1958–63.

39 Moqbel R, Hamid Q, Ying S, *et al*. Expression of mRNA and immunoreactivity for the granulocyte/macrophage colony-stimulating factor (GM-CSF) in activated human eosinophils. *J Exp Med* 1991;**174**:749–52.

40 Kita H, Ohnishi T, Okubo Y, *et al* Granulocyte/macrophage colony-stimulating factor and interleukin-3 release from human peripheral blood eosinophils and neutrophils. *J Exp Med* 1991;**174**:745–8.

41 Aubus P, Cosso B, Godard P, *et al*. Decreased suppressor cell activity of alveolar macrophages in bronchial asthma. *Am Rev Respir Dis* 1984;**130**:875–8.

42 Spiteri M, Knight RA, Jeremy JY, *et al*. Alveolar macrophage-induced suppression of T-cell hyperresponsiveness in bronchial asthma is reversed by allergen exposure. *Eur Respir J* 1994;**7**:1431–8.

43 Fischer HG, Frosch S, Reske K, *et al*. Granulocyte-macrophage colony-stimulating factor activates macrophages derived from bone marrow cultures to synthesis of MHC class II molecules and to augmented antigen presentation function. *J Immunol* 1988;**141**:3882–8.

44 Chang TL, Shea CH, Urioste S, *et al*. Heterogeneity of helper/inducer T lymphocytes: lymphokine production and lymphokine responsiveness. *J Immunol* 1990;**145**:2803–8.

45 Schleimer RP, Sterbinsky CA, Kaiser CA, *et al*. Interleukin-4 induces adherence of human eosinophils and basophils but not neutrophils to endothelium: association with expression of VCAM-1. *J Immunol* 1992;**148**:1086–92.

46 Tosi MF, Stark JM, Smith CW, *et al*. Induction of ICAM-1 expression on human airway epithelial cells by inflammatory cytokines: effects on neutrophil-epithelial cell adhesion. *Am J Respir Cell Mol Biol* 1992;**7**:214–21.

47 Brewster CEP, Howarth PH, Djukanovic R, *et al*. Myofibroblasts and subepithelial fibrosis in bronchial asthma. *Am J Respir Cell Mol Biol* 1990;**3**:507–11.

48 Hirst SJ, Barnes PJ, Twort CHL. Quantifying proliferation of cultured human and rabbit airway smooth muscle cells in response to serum and platelet-derived growth factor. *Am J Respir Cell Mol Biol* 1992;**7**:574–81.

49 Cerutis DR, Nogami M, Anderson JL, *et al*. Lysophosphatidic acid and EGF stimulate mitogenesis in human airway smooth muscle cells. *Am J Physiol* 1997;**273**:L10–5.

50 Kishimoto T, Taga T, Akira S. Cytokine signal transduction. *Cell* 1994;**76**:253–62.

51 Morgan DA, Ruscetti FW, Gallo R. Selective in vitro growth of T lymphocytes from normal human bone marrows. *Science* 1976;**193**:1007–8.

52 Levi Schaffer F, Barkans J, Newman TM, *et al*. Identification of interleukin-2 in human peripheral blood eosinophils. *Immunology* 1996;**87**:155–61.

53 Aoki Y, Qiu D, Uyei A, *et al*. Human airway epithelial cells express interleukin-2 in vitro. *Am J Physiol* 1997;**272**:L276–86.

54 Weiss A, Littman DR. Signal transduction by lymphocyte antigen receptors. *Cell* 1994;**76**:263–74.

55 Taniguchi T, Minami Y. The IL-2/IL-2 receptor system: a current overview. *Cell* 1993;**73**:5–8.

56 Hatakeyama M, Mori H, Doi T, *et al*. A restricted cytoplasmic region of IL-2 receptor beta chain is essential for growth signal transduction but not for ligand binding and internalization. *Cell* 1989;**59**:837–45.

57 Zurawski SM, Zurawski G. Receptor antagonist and selective agonist derivatives of mouse interleukin-2. *EMBO J* 1992;**11**:3905–10.

58 Smith KA. Interleukin-2: inception, impact, and implications. *Science* 1988;**240**:1169–76.

59 Lenardo MJ. Interleukin-2 programs mouse αβ T lymphocytes for apoptosis. *Nature* 1991;**353**:858–61.

60 Schorle H, Holtschke T, Hunig T, *et al*. Development and function of T cells in mice rendered interleukin-2 deficient by gene targeting. *Nature* 1991;**352**:621–4.

61 Sher ER, Leung DYM, Surs W, *et al*. Steroid-resistant asthma: cellular mechanisms contributing to inadequate response to glucocorticoid therapy. *J Clin Invest* 1994;**93**:33–9.

62 Enokihara H, Furusawa S, Nakakubo H, *et al*. T cells from eosinophilic patients produce interleukin-5 with interleukin-2 stimulation. *Blood* 1989;**73**:1809–13.

63 Nakamura Y, Ozaki T, Kamei T, *et al*. Increased granulocyte/macrophage colony-stimulating factor production by mononuclear cells from peripheral blood of patients with bronchial asthma. *Am Rev Respir Dis* 1993;**147**:87–91.

64 Rand TH, Silberstein DS, Kornfeld H, *et al*. Human eosinophils express functional interleukin 2 receptors. *J Clin Invest* 1991;**88**:825–32.

65 Macdonald D, Gordon AA, Kajitani H, *et al*. Interleukin-2 treatment-associated eosinophilia is mediated by interleukin-5 production. *Br J Haematol* 1990;**76**:168–73.

66 Sedgwick JB, Frick WE, Sandel PM, *et al*. The appearance of hypodense eosinophils during interleukin-2 treatment. *J Allergy Clin Immunol* 1990;**85**:557–66.

67 Renzi PM, Du T, Sapienza S, *et al*. Acute effects of interleukin-2 on lung mechanics and airway responsiveness in rats. *Am Rev Respir Dis* 1991;**143**:380–5.

68 Renzi PM, Sapienza S, Waserman S, *et al*. Effect of interleukin-2 on the airway response to antigen in the rat. *Am Rev Respir Dis* 1992;**146**:163–9.

69 Walker C, Bode E, Boer L, *et al*. Allergic and non-allergic asthmatics have distinct patterns of T-cell activation and cytokine production in peripheral blood and bronchoalveolar lavage. *Am Rev Respir Dis* 1992;**146**:109–15.

70 Bentley AM, Meng Q, Robinson DS, *et al*. Increases in activated T lymphocytes, eosinophils and cytokine mRNA expression for interleukin-5 and granulocyte/macrophage colony-stimulating factor in bronchial biopsies after allergen inhalation challenge in atopic asthmatics. *Am J Respir Cell Mol Biol* 1993;**8**:35–42.

71 Leung DY, Martin RJ, Szefler SJ, *et al*. Dysregulation of interleukin 4, interleukin 5, and interferon gamma gene expression in steroid-resistant asthma. *J Exp Med* 1995;**181**:33–40.

72 Corrigan CJ, Hartnell A, Kay AB. T lymphocyte activation in acute severe asthma. *Lancet* 1988;i:1129–31.

73 Elwood W, Lotvall JO, Barnes PJ, *et al*. Effect of dexamethasone and cyclosporin A on allergen-induced airway hyperresponsiveness and inflammatory cell responses in sensitized Brown-Norway rats. *Am Rev Respir Dis* 1992;**145**:1289–94.

74 Alexander AG, Barnes NC, Kay AB. Cyclosporin A in corticosteroid-dependent chronic severe asthma. *Lancet* 1992;**339**:324–7.

75 Nizankowska E, Soja J, Pinis G, *et al*. Treatment of steroid-dependent bronchial asthma with cyclosporin. *Eur Respir J* 1995;**8**:1091–9.

76 Fung MC, Hapel AJ, Ymer S, *et al*. Molecular cloning of cDNA for murine interleukin-3. *Nature* 1984;**307**:233–7.

77 Arai KI, Lee F, Miyajima A, *et al*. Cytokines: coordinators of immune and inflammatory responses. *Annu Rev Biochem* 1990;**59**:783–836.

78 Hayashida K, Kitamura T, Gorman DM, *et al*. Molecular cloning of a second subunit of the receptor for human granulocyte-macrophage colony-stimulating factor (GM-CSF): reconstitution of a high-affinity GM-CSF receptor. *Proc Natl Acad Sci USA* 1990;**87**:9655–9.

79 Sorensen P, Mui AL, Krystal G. Interleukin-3 stimulates the tyrosine phosphorylation of the 140-kilodalton interleukin-3 receptor. *J Biol Chem* 1989;**264**:19253–8.

80 Isfort R, Huhn RD, Frackelton AR, *et al*. Stimulation of factor-dependent myeloid cell lines with interleukin 3 induces tyrosine phosphorylation of several cellular substrates. *J Biol Chem* 1988;**263**:19203–9.

81 Sun Q, Woodcock JM, Rapoport A, *et al*. Monoclonal antibody 7G3 recognizes the N-terminal domain of the human interleukin-3 (IL-3) receptor alpha-chain and functions as a specific IL-3 receptor antagonist. *Blood* 1996;**87**:83–92.

82 Korpelainen EI, Gamble JR, Smith WB, *et al*. The receptor for interleukin 3 is selectively induced in human endothelial cells by tumor necrosis factor alpha and potentiates interleukin 8 secretion and neutrophil transmigration (see comments). *Proc Natl Acad Sci USA* 1993;**90**:11137–41.

83 Ottmann OG, Abboud M, Welte K, *et al*. Stimulation of human hematopoietic progenitor cell proliferation and differentiation by recombinant human interleukin 3. Comparison and interactions with recombinant human granulocyte-macrophage and granulocyte colony-stimulating factors. *Exp Hematol* 1989;**17**:191–7.

84 Smith WB, Guida L, Sun Q, *et al*. Neutrophils activated by granulocyte-macrophage colony-stimulating factor express receptors for interleukin-3 which mediate class II expression. *Blood* 1995;**86**:3938–44.

85 Dent LA, Strath M, Mellor AL, *et al*. Eosinophilia in transgenic mice expressing interleukin 5. *J Exp Med* 1990;**172**: 1425–31.

86 Robinson DS, Hamid Q, Bentley AM, *et al*. Activation of CD4+ T cells and increased IL-4, IL-5 and GM-CSF mRNA positive cells in bronchoalveolar lavage fluid (BAL) 24 hours after allergen inhalation challenge of atopic asthmatic patients. *J Allergy Clin Immunol* 1993;**92**:313–24.

87 Blotta MH, Marshall JD, DeKruyff RH, *et al*. Cross-linking of the CD40 ligand on human CD4+ T lymphocytes generates a costimulatory signal that up-regulates IL-4 synthesis. *J Immunol* 1996;**156**:3133–40.

88 Blotta MH, DeKruyff RH, Umetsu DT. Corticosteroids inhibit IL-12 production in human monocytes and enhance their capacity to induce IL-4 synthesis in CD4+ lymphocytes. *J Immunol* 1997;**158**:5589–95.

89 Ohara J, Paul WE. Receptors for B-cell stimulatory factor-1 expressed on cells of haematopoietic lineage. *Nature* 1987; **325**:537–40.

90 Park LS, Friend D, Sassenfeld HM, *et al*. Characterization of the human B cell stimulatory factor 1 receptor. *J Exp Med* 1987;**166**:476–88.

91 Park LS, Friend D, Grabstein K, *et al*. Characterization of the high-affinity cell-surface receptor for murine B-cell-stimulating factor 1. *Proc Natl Acad Sci USA* 1987;**84**: 1669–73.

92 Idzerda RL, March CJ, Mosley B, *et al*. Human interleukin 4 receptor confers biological responsiveness and defines a novel receptor superfamily. *J Exp Med* 1990;**171**:861–73.

93 Galizzi JP, Zuber CE, Harada N, *et al*. Molecular cloning of a cDNA encoding the human interleukin 4 receptor. *Int Immunol* 1990;**2**:669–75.

94 Kondo M, Takeshita T, Ishii N, *et al*. Sharing of the interleukin-2 (IL-2) receptor gamma chain between receptors for IL-2 and IL-4. *Science* 1993;**262**:1874–7.

95 Russell SM, Keegan AD, Harada N, *et al*. Interleukin-2 receptor gamma chain: a functional component of the interleukin-4 receptor. *Science* 1993;**262**:1880–3.

96 Garrone P, Djossou O, Galizzi JP, *et al*. A recombinant extracellular domain of the human interleukin 4 receptor inhibits the biological effects of interleukin 4 on T and B lymphocytes. *Eur J Immunol* 1991;**21**:1365–9.

97 Fanslow WC, Spriggs MK, Rauch CT, *et al*. Identification of a distinct low-affinity receptor for human interleukin-4 on pre-B cells. *Blood* 1993;**81**:2998–3005.

98 Kotsimbos TC, Ghaffar O, Minshall EM, *et al*. Expression of the IL-4 receptor alpha-subunit is increased in bronchial biopsy specimens from atopic and nonatopic asthmatic subjects. *J Allergy Clin Immunol* 1998;**102**:859–66.

99 Wang LM, Keegan AD, Paul WE, *et al*. IL-4 activates a distinct signal transduction cascade from IL-3 in factor-dependent myeloid cells. *EMBO J* 1992;**11**:4899–908.

100 Wang LM, Keegan AD, Li W, *et al*. Common elements in interleukin 4 and insulin signaling pathways in factor-dependent hematopoietic cells. *Proc Natl Acad Sci USA* 1993;**90**:4032–6.

101 Hatakeyama M, Kono T, Kobayashi N, *et al*. Interaction of the IL-2 receptor with the src-family kinase p56lck: identification of novel intermolecular association. *Science* 1991; **252**:1523–8.

102 Imani F, Rager KJ, Catipovic B, *et al*. Interleukin-4 (IL-4) induces phosphatidylinositol 3-kinase (p85) dephosphorylation. Implications for the role of SHP-1 in the IL-4-induced signals in human B cells. *J Biol Chem* 1997;**272**:7927–31.

103 Shimoda K, van Deursen J, Sangster MY, *et al*. Lack of IL-4-induced Th2 response and IgE class switching in mice with disrupted Stat6 gene. *Nature* 1996;**380**:630–3.

104 Takeda K, Tanaka T, Shi W, *et al*. Essential role of Stat6 in IL-4 signalling. *Nature* 1996;**380**:627–30.

105 Finney M, Guy GR, Michell RH, *et al*. Interleukin 4 activates human B lymphocytes via transient inositol lipid hydrolysis and delayed cyclic adenosine monophosphate generation. *Eur J Immunol* 1990;**20**:151–6.

106 Esswein LA, Hershey GK, Friedrich MF, *et al*. The association of atopy with a gain-of-function mutation in the α-subunit of the IL-4 receptor. *N Engl J Med* 1997;**337**: 1720–5.

107 Paulson RF, Vesely S, Siminovitch KA, *et al*. Signalling by the W/Kit receptor tyrosine kinase is negatively regulated in vivo by the protein tyrosine phosphatase Shp1. *Nature Genet* 1996;**13**:309–15.

108 Swain SL, Weinberg AD, English M, *et al*. IL-4 directs the development of Th2-like helper effectors. *J Immunol* 1990; **145**:3796–806.

109 Le Gros G, Ben-Sasson SZ, Seder RA, *et al*. Generation of interleukin 4 (IL-4)-producing cells in vivo and in vitro: IL-2 and IL-4 are required for in vitro generation of IL-4-producing cells. *J Exp Med* 1990;**172**:921–9.

110 Coyle AJ, Erard F, Bertrand C, *et al*. Virus-specific CD8+ cells can switch to interleukin 5 production and induce airway eosinophilia. *J Exp Med* 1995;**181**:1229–33.

111 Postlethwaite AE, Seyer JM. Fibroblast chemotaxis induction by human recombinant interleukin-4: identification by synthetic peptide analysis of two chemotactic domains residing in aminoacid sequences 70–78 and 89–122. *J Clin Invest* 1991;**87**:2147–52.

112 Postlethwaite AE, Holness MA, Katai H, *et al*. Human fibroblasts synthesizes elevated levels of extracellular matrix proteins in response to interleukin 4. *J Clin Invest* 1992;**90**:1479–85.

113 Favre C, Saeland S, Caux C, *et al*. Interleukin 4 has basophilic and eosinophilic cells growth-promoting activity on cord blood cells. *Blood* 1990;**75**:67–73.

114 Lacraz S, Nicod L, Galve de Rochemonteix BE, *et al*. Suppression of metalloproteinase biosynthesis in human alveolar macrophages by interleukin-4. *J Clin Invest* 1992;**90**: 382–8.

115 Berkman N, Robichaud A, Robbins RA, *et al*. Inhibition of inducible nitric oxide synthase in human bronchial epithelial cell line by IL-4 and IL-13. *Immunology* 1996;**89**:363–7.

116 John M, Hirst SJ, Jose PJ, *et al*. Human airway smooth muscle cells express and release RANTES in response to Th-1 cytokines: regulation by Th-2 cytokines and corticosteroids. *J Immunol* 1997;**158**:1841–7.

117 John M, Au BT, Jose PJ, *et al*. Expression and release of interleukin-8 by human airway smooth muscle cells: inhibition by Th-2 cytokines and corticosteroids. *Am J Respir Cell Mol Biol* 1998;**18**:84–90.

118 Ying S, Humbert M, Barkans J, *et al*. Expression of IL-4 and IL-5 mRNA and protein product by CD4+ and CD8+ T cells, eosinophils, and mast cells in bronchial biopsies obtained from atopic and nonatopic (intrinsic) asthmatics. *J Immunol* 1997;**158**:3539–44.

119 Bradding P, Feather IH, Howarth PH, *et al*. Interleukin 4 is localized to and released by human mast cells. *J Exp Med* 1992;**176**:1381–6.

120 Brusselle GG, Kips JC, Tavernier JH, *et al*. Attenuation of allergic airway inflammation in IL-4 deficient mice. *Clin Exp Allergy* 1994;**24**:73–80.

121 Brusselle G, Kips J, Joos G, *et al*. Allergen-induced airway inflammation and bronchial responsiveness in wild-type and interleukin-4-deficient mice. *Am J Respir Cell Mol Biol* 1995;**12**:254–9.

122 Coyle AJ, Le Gros G, Bertrand C, *et al*. Interleukin-4 is required for the induction of lung Th2 mucosal immunity. *Am J Respir Cell Mol Biol* 1995;**13**:54–9.

123 Corry DB, Folkesson HG, Warnock ML, *et al*. Interleukin 4, but not interleukin 5 or eosinophils, is required in a murine model of acute airway hyperreactivity. *J Exp Med* 1996;**183**:109–17.

124 Gavett SH, O'Hearn DJ, Karp CL, *et al*. Interleukin-4 receptor blockade prevents airway responses induced by antigen challenge in mice. *Am J Physiol* 1997;**272**:L253–61.

125 Shi HZ, Deng JM, Xu H, *et al*. Effect of inhaled interleukin-4 on airway hyperreactivity in asthmatics. *Am J Respir Crit Care Med* 1998;**157**:1818–21.

126 Temann UA, Prasad B, Gallup MW, *et al*. A novel role for murine IL-4 in vivo: induction of MUC5AC gene expression and mucin hypersecretion. *Am J Respir Cell Mol Biol* 1997;**16**:471–8.

127 Lopez AF, Begley CG, Williamson DJ, *et al*. Murine eosinophil differentiation factor. An eosinophil-specific colony-stimulating factor with activity for human cells. *J Exp Med* 1986;**163**:1085–99.

128 Hamid Q, Azzawi M, Sun Ying, *et al*. Expression of mRNA for interleukin-5 in mucosal bronchial biopsies from asthma. *J Clin Invest* 1991;**87**:1541–9.

129 Till S, Li B, Durham S, *et al*. Secretion of the eosinophil-active cytokines interleukin-5, granulocyte/macrophage colony-stimulating factor and interleukin-3 by bronchoalveolar lavage CD4+ and CD8+ T cell lines in atopic asthmatics, and atopic and non-atopic controls. *Eur J Immunol* 1995;**25**:2727–31.

130 Dubucquoi S, Desreumaux P, Janin A, *et al*. Interleukin 5 synthesis by eosinophils: association with granules and immunoglobulin-dependent secretion. *J Exp Med* 1994; **179**:703–8.

131 Broide D, Paine MM, Firestein GS. Eosinophils express interleukin 5 and granulocyte-macrophage colony-stimulating factor mRNA at sites of allergic inflammation in asthmatics. *J Clin Invest* 1992;**90**:1414–24.

132 Sedgewick JB, Calhoun WJ, Gleich GJ, *et al*. Immediate and late airway response of allergic rhinitis patients to segmental antigen challenge. Characterization of eosinophil and mast cell mediators. *Am Rev Respir Dis* 1991;**144**: 1274–81.

133 Ohnishi T, Kita H, Weiler D, *et al*. IL-5 is the predominant eosinophil-active cytokine in the antigen-induced pulmonary late-phase reaction. *Am Rev Respir Dis* 1993;**147**:901–7.

134 Ohnishi T, Collins DS, Sur S, *et al*. IgE-mediated release of eosinophil viability enhancing activity in the lung in vivo. Identification as interleukin-5 and association with eosinophil recruitment and degranulation. *J Allergy Clin Immunol* 1993;**92**:607–15.

135 Corrigan CJ, Haczku A, Gemou-Engesaeth V, *et al*. CD4 T-lymphocyte activation in asthma is accompanied by increased serum concentration of interleukin-5: effect of glucocorticoid therapy. *Am Rev Respir Dis* 1993;**147**:540–7.

136 Keatings VM, O'Connor BJ, Wright LG, *et al*. Late response to allergen is associated with increased concentra-

tions of tumor necrosis factor-alpha and IL-5 in induced sputum. *J Allergy Clin Immunol* 1997;**99**:693–8.

137 Stranick KS, Zambas DN, Uss AS, *et al*. Identification of transcription factor binding sites important in the regulation of the human interleukin-5 gene. *J Biol Chem* 1997;**272**:16453–65.

138 Lopez AF, Vadas MA, Woodcock JM, *et al*. Interleukin-5, interleukin-3, and granulocyte-macrophage colony-stimulating factor cross-compete for binding to cell surface receptors on human eosinophils. *J Biol Chem* 1991;**266**: 24741–7.

139 Tavernier J, Devos R, Cornelis S, *et al*. A human high affinity interleukin-5 receptor (IL5R) is composed of an IL5-specific α chain and β chain with the receptor for GM-CSF. *Cell* 1991;**66**:1175–84.

140 Bazan JF. Structural design and molecular evolution of a cytokine receptor superfamily. *Proc Natl Acad Sci USA* 1990;**87**:6934–8.

141 Tavernier J, Tuypens T, Verhee A, *et al*. Identification of receptor-binding domains on human interleukin 5 and design of an interleukin 5-derived receptor antagonist. *Proc Natl Acad Sci USA* 1995;**92**:5194–8.

142 Tavernier J, Tuypens T, Plaetinck G, *et al*. Molecular basis of the membrane-anchored and two soluble isoforms of the human interleukin 5 receptor alpha subunit. *Proc Natl Acad Sci USA* 1992;**89**:7041–5.

143 Koike M, Takatsu K. IL-5 and its receptor: which role do they play in the immune response? *Int Arch Allergy Immunol* 1994;**104**:1–9.

144 Devos R, Guisez Y, Cornelis S, *et al*. Recombinant soluble human interleukin-5 (hIL-5) receptor molecules. Cross-linking and stoichiometry of binding to IL-5. *J Biol Chem* 1993;**268**:6581–7.

145 Yasruel Z, Humbert M, Kotsimbos TC, *et al*. Membrane-bound and soluble alpha IL-5 receptor mRNA in the bronchial mucosa of atopic and nonatopic asthmatics. *Am J Respir Crit Care Med* 1997;**155**:1413–8.

146 Sehmi R, Wood LJ, Watson R, *et al*. Allergen-induced increases in IL-5 receptor alpha-subunit expression on bone marrow-derived CD34+ cells from asthmatic subjects. A novel marker of progenitor cell commitment towards eosinophilic differentiation. *J Clin Invest* 1997;**100**: 2466–75.

147 Adachi T, Alam R. The mechanism of IL-5 signal transduction. *Am J Physiol* 1998;**275**:C623–33.

148 Lopez AF, Sanderson CJ, Gamble JR, *et al*. Recombinant human interleukin 5 is a selective activator of human eosinophil function. *J Exp Med* 1988;**167**:219–24.

149 Clutterbuck EJ, Hirst EM, Sanderson CJ. Human interleukin-5 (IL-5) regulates the production of eosinophils in human bone marrow cultures: comparison and interaction with IL-1, IL-3, IL-6 and GM-CSF. *Blood* 1989;**73**: 1504–12.

150 Yamaguchi Y, Hayashi Y, Sugama Y, *et al*. Highly purified murine interleukin 5 (IL-5) stimulates eosinophil function and prolongs in vitro survival. IL-5 as an eosinophil factor. *J Exp Med* 1988;**167**:1737–40.

151 Iwama T, Nagai H, Suda H, *et al*. Effect of murine recombinant interleukin-5 on the cell population in guinea-pig airways. *Br J Pharmacol* 1992;**105**:19–22.

152 Rothenberg ME, Ownbey R, Mehlhop PD, *et al*. Eotaxin triggers eosinophil-selective chemotaxis and calcium flux via a distinct receptor and induces pulmonary eosinophilia in the presence of interleukin 5 in mice. *Mol Med* 1996;**2**:334–48.

153 Shi H, Qin S, Huang G, *et al*. Infiltration of eosinophils into the asthmatic airways caused by interleukin 5. *Am J Respir Cell Mol Biol* 1997;**16**:220–4.

154 Shi HZ, Xiao CQ, Zhong D, *et al*. Effect of inhaled interleukin-5 on airway hyperreactivity and eosinophilia in asthmatics. *Am J Respir Crit Care Med* 1998;**157**:204–9.

155 Venge J, Lampinen M, Hakansson L, *et al*. Identification of IL-5 and RANTES as the major eosinophil chemoattractants in the asthmatic lung. *J Allergy Clin Immunol* 1996;**97**: 1110–5.

156 Rothenberg ME, MacLean JA, Pearlman E, *et al*. Targeted disruption of the chemokine eotaxin partially reduces antigen-induced tissue eosinophilia. *J Exp Med* 1997;**185**: 785–90.

157 Mauser PJ, Pitman AM, Fernandez X, *et al*. Effects of an antibody to interleukin-5 in a monkey model of asthma. *Am J Respir Crit Care Med* 1995;**152**:467–72.

158 Mauser PJ, Pitman A, Witt A, *et al*. Inhibitory effect of the TRFK-5 anti-IL-5 antibody in a guinea pig model of asthma. *Am Rev Respir Dis* 1993;**148**:1623–7.

159 van Oosterhout AJM, Rudolf A, Ladenius C, *et al*. Effect of anti-IL-5 and IL-5 in airway hyperreactivity and eosinophils in guinea pigs. *Am Rev Respir Dis* 1993;**147**:548–52.

160 Chand N, Harrison JE, Rooney S, *et al*. Anti IL-5 monoclonal antibody inhibits allergic late phase bronchial eosinophilia in guinea pigs: a therapeutic approach. *Eur J Pharmacol* 1992;**211**:121–3.

161 Foster PS, Hogan SP, Ramsay AJ, *et al*. Interleukin 5 deficiency abolishes eosinophilia, airways hyperreactivity, and lung damage in a mouse asthma model (see comments). *J Exp Med* 1996;**183**:195–201.

162 Lee JJ, McGarry MP, Farmer SC, *et al*. Interleukin-5 expression in the lung epithelium of transgenic mice leads to pulmonary changes pathognomonic of asthma. *J Exp Med* 1997;**185**:2143–56.

163 Wang CH, Liu CY, Lin HC, *et al*. Increased exhaled nitric oxide in active pulmonary tuberculosis due to inducible NO synthase upregulation in alveolar macrophages. *Eur Respir J* 1998;**11**:809–15.

164 Minshall EM, Schleimer R, Cameron L, *et al*. Interleukin-5 expression in the bone marrow of sensitized Balb/c mice after allergen challenge. *Am J Respir Crit Care Med* 1998;**158**:951–7.

165 Mould AW, Matthaei KI, Young IG, *et al*. Relationship between interleukin-5 and eotaxin in regulating blood and tissue eosinophilia in mice. *J Clin Invest* 1997;**99**:1064–71.

166 Robinson DS, Hamid Q, Ying S, *et al*. Prednisolone treatment in asthma is associated with modulation of bronchoalveolar lavage cell IL-4, IL-5 and IFN-γ cytokine gene expression. *Am Rev Respir Dis* 1993;**148**:401–6.

167 Rolfe FG, Valentine JE, Sewell WA. Cyclosporin A and FK506 reduce interleukin-5 mRNA abundance by inhibiting gene transcription. *Am J Respir Cell Mol Biol* 1997;**17**:243–50.

168 Uyttenhove C, Simpson RJ, van Snick J. Functional and structural characterization of P40, a mouse glycoprotein with T-cell growth factor activity. *Proc Natl Acad Sci USA* 1988;**85**:6934–8.

169 Renauld JC, Kermouni A, Vink A, *et al*. Interleukin-9 and its receptor: involvement in mast cell differentiation and T cell oncogenesis. *J Leukoc Biol* 1995;**57**:353–60.

170 Houssiau FA, Mascart-Lemone F, Stevens M, *et al*. IL-12 inhibits in vitro immunoglobulin production by human lupus peripheral blood mononuclear cells (PBMC). *Clin Exp Immunol* 1997;**108**:375–80.

171 Monteyne P, Renauld JC, Van Broeck J, *et al* IL-4-independent regulation of in vivo IL-9 expression. *J Immunol* 1997;**159**:2616–23.

172 Renauld JC, Goethals A, Houssiau F, *et al*. Human P40/IL-9. Expression in activated CD4+ T cells, genomic organization, and comparison with the mouse gene. *J Immunol* 1990;**144**:4235–41.

173 Grencis RK, Hultner L, Else KJ. Host protective immunity to *Trichinella spiralis* in mice: activation of Th cell subsets and lymphokine secretion in mice expressing different response phenotypes. *Immunology* 1991;**74**:329–32.

174 Houssiau FA, Renauld JC, Stevens M, *et al*. Human T cell lines and clones respond to IL-9. *J Immunol* 1993;**150**: 2634–40.

175 Schmitt E, Van Brandwijk R, van Snick J, *et al*. TCGF III/P40 is produced by naive murine CD4+ T cells but is not a general T cell growth factor. *Eur J Immunol* 1989;**19**:2167–70.

176 Dugas B, Renauld JC, Pene J, *et al*. Interleukin-9 potentiates the interleukin-4-induced immunoglobulin (IgG, IgM and IgE) production by normal human B lymphocytes. *Eur J Immunol* 1993;**23**:1687–92.

177 Hultner L, Druez C, Moeller J, *et al*. Mast cell growth-enhancing activity (MEA) is structurally related and functionally identical to the novel mouse T cell growth factor P40/TCGFIII (interleukin 9). *Eur J Immunol* 1990;**20**:1413–6.

178 Eklund KK, Ghildyal N, Austen KF, *et al*. Induction by IL-9 and suppression by IL-3 and IL-4 of the levels of chromosome 14-derived transcripts that encode late-expressed mouse mast cell proteases. *J Immunol* 1993;**151**: 4266–73.

179 Donahue RE, Yang YC, Clark SC. Human P40 T-cell growth factor (interleukin-9) supports erythroid colony formation. *Blood* 1990;**75**:2271–5.

180 Williams DE, Morrissey PJ, Mochizuki DY, *et al*. T-cell growth factor P40 promotes the proliferation of myeloid cell lines and enhances erythroid burst formation by normal murine bone marrow cells in vitro. *Blood* 1990;**76**: 906–11.

181 Godfraind C, Louahed J, Faulkner H, *et al*. Intraepithelial infiltration by mast cells with both connective tissue-type and mucosal-type characteristics in gut, trachea, and kidneys of IL-9 transgenic mice. *J Immunol* 1998;**160**: 3989–96.

182 Louahed J, Kermouni A, van Snick J, *et al*. IL-9 induces expression of granzymes and high-affinity IgE receptor in murine T helper clones. *J Immunol* 1995;**154**:5061–70.

183 Renauld JC, van der Lugt N, Vink A, *et al*. Thymic lymphomas in interleukin 9 transgenic mice. *Oncogene* 1994;**9**:1327–32.

184 Temann UA, Geba GP, Rankin JA, *et al*. Expression of interleukin 9 in the lungs of transgenic mice causes airway inflammation, mast cell hyperplasia, and bronchial hyperresponsiveness. *J Exp Med* 1998;**188**:1307–20.

185 McLane MP, Haczku A, van de Rijn M, *et al*. Interleukin-9 promotes allergen-induced eosinophilic inflammation and airway hyperresponsiveness in transgenic mice. *Am J Respir Cell Mol Biol* 1998;**19**:713–20.

186 Doull IJ, Lawrence S, Watson M, *et al*. Allelic association of gene markers on chromosomes 5q and 11q with atopy and bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 1996;**153**:1280–4.

187 Nicolaides NC, Holroyd KJ, Ewart SL, *et al*. Interleukin 9: a candidate gene for asthma. *Proc Natl Acad Sci USA* 1997; **94**:13175–80.

188 Grasso L, Huang M, Sullivan CD, *et al*. Molecular analysis of human interleukin-9 receptor transcripts in peripheral blood mononuclear cells. Identification of a splice variant encoding for a nonfunctional cell surface receptor. *J Biol Chem* 1998;**273**:24016–24.

189 Holroyd KJ, Martinati LC, Trabetti E, *et al*. Asthma and bronchial hyperresponsiveness linked to the XY long arm pseudoautosomal region. *Genomics* 1998;**52**:233–5.

190 Minty A, Chalon P, Derocq J-M, *et al*. Interleukin-13 is a new human lymphokine regulating inflammatory and immune responses. *Nature* 1993;**362**:248–50.

191 Zurawski G, De Vries JE. Interleukin 13, an interleukin 4-like cytokine that acts on monocytes and B cells, but not on T cells. *Immunol Today* 1994;**15**:19–26.

192 Zurawski SM, Vega FJ, Huyghe B, *et al*. Receptors for interleukin-13 and interleukin-4 are complex and share a novel component that functions in signal transduction. *EMBO J* 1993;**12**:2663–70.

193 Aman MJ, Tayebi N, Obiri NI, *et al*. cDNA cloning and characterization of the human interleukin 13 receptor alpha chain. *J Biol Chem* 1996;**271**:29265–70.

194 McKenzie ANJ, Culpepper JA, de Waal Malefyt R, *et al*. Interleukin 13, a T-cell-derived cytokine that regulates human monocyte and B-cell function. *Proc Natl Acad Sci USA* 1993;**90**:3735–9.

195 Doucet C, Brouty-Boye D, Pottin-Clemenceau C, *et al*. IL-4 and IL-13 specifically increase adhesion molecule and inflammatory cytokine expression in human lung fibroblasts. *Int Immunol* 1998;**10**:1421–33.

196 Zurawski SM, Vega FJ, Huyghe B, *et al*. Receptors for interleukin-13 and interleukin-4 are complex and share a novel component that functions in signal transduction. *EMBO J* 1993;**12**:2663–70.

197 de Waal Malefyt R, Figdor CG, Huijbens R, *et al*. Effects of IL-13 on phenotype, cytokine production, and cytotoxic function of human monocytes. *J Immunol* 1993;**151**:6370–81.

198 Berkman N, Roesems G, Jose PJ, *et al*. Interleukin-13 inhibits expression of macrophage-inflammatory protein-1α from human blood monocytes and alveolar macrophages. *Am J Respir Cell Mol Biol* 1995;**13**:382–9.

199 Yanagawa H, Sone S, Haku T, *et al*. Contrasting effect of interleukin-13 on interleukin-1 receptor antagonist and proinflammatory cytokine production by human alveolar macrophages. *Am J Respir Cell Mol Biol* 1995;**12**:71–6.

200 Hsieh C-S, Macatonia SE, Tripp CA, *et al*. Development of TH1 CD4+ T cells through IL-12 produced by Listeria-induced macrophages. *Science* 1994;**15**:547–9.

201 Spahn JD, Szefler SJ, Surs W, *et al*. A novel action of IL-13: induction of diminished monocyte glucocorticoid receptor-binding affinity. *J Immunol* 1996;**157**:2654–9.

202 Luttmann W, Knoechel B, Foerster M, *et al*. Activation of human eosinophils by IL-13. Induction of CD69 surface antigen, its relationship to messenger RNA expression, and promotion of cellular viability. *J Immunol* 1996;**157**:1678–83.

203 Cocks BG, de Waal Malefyt R, Galizzi JP, *et al*. IL-13 induces proliferation and differentiation of human B cells activated by the CD40 ligand. *Int Immunol* 1993;**6**:657–63.

204 Punnonen J, Aversa G, Cocks BG, *et al*. Interleukin 13 induces interleukin 4-independent IgG4 and IgE synthesis and CD23 expression by human B cells. *Proc Natl Acad Sci USA* 1993;**90**:3730–4.

205 Aversa G, Punnonen J, Cocks BG, *et al*. An interleukin 4 (IL-4) mutant protein inhibits both IL-4 or IL-13-induced human immunoglobulin G4 (IgG4) and IgE synthesis and B cell proliferation: support for a common component shared by IL-4 and IL-13 receptors. *J Exp Med* 1993;**178**:2213–8.

206 Naseer T, Minshall EM, Leung DY, *et al*. Expression of IL-12 and IL-13 mRNA in asthma and their modulation in response to steroid therapy. *Am J Respir Crit Care Med* 1997;**155**:845–51.

207 Humbert M, Durham SR, Kimmitt P, *et al*. Elevated expression of messenger ribonucleic acid encoding IL-13 in the bronchial mucosa of atopic and nonatopic subjects with asthma. *J Allergy Clin Immunol* 1997;**99**:657–65.

208 Kroegel C, Julius P, Matthys H, *et al*. Endobronchial secretion of interleukin-13 following local allergen challenge in atopic asthma: relationship to interleukin-4 and eosinophil counts. *Eur Respir J* 1996;**9**:899–904.

209 Wills-Karp M, Luyimbazi J, Xu X, *et al*. Interleukin-13: central mediator of allergic asthma. *Science* 1998;**282**:2258–61.

210 Grunig G, Warnock M, Wakil AE, *et al*. Requirement for IL-13 independently of IL-4 in experimental asthma. *Science* 1998;**282**:2261–3.

211 Grabstein KH, Eisenman J, Shanebeck K, *et al*. Cloning of a T cell growth factor that interacts with the beta chain of the interleukin-2 receptor. *Science* 1994;**264**:965–8.

212 Jonuleit H, Wiedemann K, Muller G, *et al*. Induction of IL-15 messenger RNA and protein in human blood-derived dendritic cells: a role for IL-15 in attraction of T cells. *J Immunol* 1997;**158**:2610–5.

213 Badolato R, Ponzi AN, Millesimo M, *et al*. Interleukin-15 (IL-15) induces IL-8 and monocyte chemotactic protein 1 production in human monocytes. *Blood* 1997;**90**:2804–9.

214 Treiber Held S, Stewart DM, Kurman CC, *et al*. IL-15 induces the release of soluble IL-2Rα from human peripheral blood mononuclear cells. *Clin Immunol Immunopathol* 1996;**79**:71–8.

215 Angiolillo AL, Kanegane H, Sgadari C, *et al*. Interleukin-15 promotes angiogenesis in vivo. *Biochem Biophys Res Commun* 1997;**233**:231–7.

216 Girard D, Paquet ME, Paquin R, *et al*. Differential effects of interleukin-15 (IL-15) and IL-2 on human neutrophils: modulation of phagocytosis, cytoskeleton rearrangement, gene expression, and apoptosis by IL-15. *Blood* 1996;**88**:3176–84.

217 Mori A, Suko M, Kaminuma O, *et al*. IL-15 promotes cytokine production of human T helper cells. *J Immunol* 1996;**156**:2400–5.

218 Wilkinson PC, Liew FY. Chemoattraction of human blood T lymphocytes by interleukin-15. *J Exp Med* 1995;**181**:1255–9.

219 Center DM, Cruikshank W. Modulation of lymphocyte migration by human lymphokines. I. Identification and characterization of chemoattractant activity for lymphocytes from mitogen-stimulated mononuclear cells. *J Immunol* 1982;**128**:2563–8.

220 Center DM, Cruikshank WW, Berman JS, *et al*. Functional characteristics of histamine receptor-bearing mononuclear cells. I. Selective production of lymphocyte chemoattractant lymphokines with histamine used as a ligand. *J Immunol* 1983;**131**:1854–9.

221 Laberge S, Cruikshank WW, Beer DJ, *et al*. Secretion of IL-16 (lymphocyte chemoattractant factor) from serotonin-stimulated CD8+ T cells in vitro. *J Immunol* 1996;**156**:310–5.

222 Laberge S, Cruikshank WW, Kornfeld H, *et al*. Histamine-induced secretion of lymphocyte chemoattractant factor from CD8+ T cells is independent of transcription and translation. Evidence for constitutive protein synthesis and storage. *J Immunol* 1995;**155**:2902–10.

223 Bellini A, Yoshimura H, Vittori E, *et al*. Bronchial epithelial cells of patients with asthma release chemoattractant factors for T lymphocytes. *J Allergy Clin Immunol* 1993;**92**:412–24.

224 Lim KG, Wan HC, Bozza PT, *et al*. Human eosinophils elaborate the lymphocyte chemoattractants IL-16 (lymphocyte chemoattractant factor) and RANTES. *J Immunol* 1996;**156**:2566–70.

225 Rumsaeng V, Cruikshank WW, Foster B, *et al*. Human mast cells produce the CD4+ T lymphocyte chemoattractant factor, IL-16. *J Immunol* 1997;**159**:2904–10.

226 Cruikshank WW, Center DM, Nisar N, *et al*. Molecular and functional analysis of a lymphocyte chemoattractant factor: association of biologic function with CD4 expression. *Proc Natl Acad Sci USA* 1994;**91**:5109–113.

227 Rand TH, Cruikshank WW, Center DM, *et al*. CD4-mediated stimulation of human eosinophils: lymphocyte chemoattractant factor and other CD4-binding ligands elicit eosinophil migration. *J Exp Med* 1991;**173**:1521–8.

228 Cruikshank WW, Berman JS, Theodore AC, *et al*. Lymphokine activation of T4+ T lymphocytes and monocytes. *J Immunol* 1987;**138**:3817–23.

229 Cruikshank WW, Long A, Torpy RE, *et al*. Early identification of IL-16 (lymphocyte chemoattractant factor) and macrophage inflammatory protein 1 α (MIP-1α) in bronchoalveolar lavage fluid of antigen-challenged asthma. *Am J Respir Cell Mol Biol* 1995;**13**:738–47.

230 Mashikian MV, Tarpy RE, Saukkonen JJ, *et al*. Identification of IL-16 as the lymphocyte chemotactic activity in the bronchoalveolar lavage fluid of histamine-challenged asthmatic patients. *J Allergy Clin Immunol* 1998;**101**:786–92.

231 Laberge S, Ernst P, Ghaffar O, *et al*. Increased expression of interleukin-16 in bronchial mucosa of subjects with atopic asthma. *Am J Respir Cell Mol Biol* 1997;**17**:193–202.

232 Hessel EM, Cruikshank WW, van Ark I, *et al*. Involvement of IL-16 in the induction of airway hyper-responsiveness and up-regulation of IgE in a murine model of allergic asthma. *J Immunol* 1998;**160**:2998–3005.

233 Yao Z, Fanslow WC, Seldin MF, *et al*. Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. *Immunity* 1995;**3**:811–21.

234 Yao Z, Painter SL, Fanslow WC, *et al*. Human IL-17: a novel cytokine derived from T cells. *J Immunol* 1995;**155**:5483–6.

235 Fossiez F, Djossou O, Chomarat P, *et al*. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines (see comments). *J Exp Med* 1996;**183**:2593–603.

236 Attur MG, Patel RN, Abramson SB, *et al* Interleukin-17 upregulation of nitric oxide production in human osteoarthritis cartilage. *Arthritis Rheum* 1997;**40**:1050–3.

237 Ushio S, Namba M, Okura T, *et al*. Cloning of the cDNA for human IFN-gamma-inducing factor, expression in *Escherichia coli*, and studies on the biologic activities of the protein. *J Immunol* 1996;**156**:4274–9.

238 Torigoe K, Ushio S, Okura T, *et al*. Purification and characterization of the human interleukin-18 receptor. *J Biol Chem* 1997;**272**:25737–42.

239 Xu D, Chan WL, Leung BP, *et al*. Selective expression and functions of interleukin 18 receptor on T helper (Th) type 1 but not Th2 cells. *J Exp Med* 1998;**188**:1485–92.

240 Puren AJ, Fantuzzi G, Gu Y, *et al*. Interleukin-18 (IFNγ-inducing factor) induces IL-8 and IL-1β via TNF-α production from non-CD14+ human blood mononuclear cells. *J Clin Invest* 1998;**101**:711–21.

241 Tsuji Takayama K, Matsumoto S, Koide K, *et al*. Interleukin-18 induces activation and association of p56(lck) and MAPK in a murine TH1 clone. *Biochem Biophys Res Commun* 1997;**237**:126–30.

242 Matsumoto S, Tsuji Takayama K, Aizawa Y, *et al*. Interleukin-18 activates NF-kappaB in murine T helper type 1 cells. *Biochem Biophys Res Commun* 1997;**234**:454–7.

243 Yoshimoto T, Okamura H, Tagawa YI, *et al*. Interleukin 18 together with interleukin 12 inhibits IgE production by induction of interferon-gamma production from activated B cells. *Proc Natl Acad Sci USA* 1997;**94**:3948–53.

244 Cerretti DP, Kozlosky CJ, Mosley B, *et al*. Molecular cloning of the interleukin-1 beta converting enzyme. *Science* 1992;**256**:97–100.

245 Thornberry NA, Bull HG, Calaycay JR, *et al*. A novel heterodimeric cysteine protease is required for interleukin-1 beta processing in monocytes. *Nature* 1992;**356**:768–74.

246 March CJ, Mosley B, Larsen A, *et al*. Cloning, sequence and expression of two distinct human interleukin-1 complementary DNAs. *Nature* 1985;**315**:641–7.

247 Nishida T, Nishino N, Takano M, *et al*. cDNA cloning of IL-1 alpha and IL-1 beta from mRNA of U937 cell line. *Biochem Biophys Res Commun* 1987;**143**:345–52.

248 Weller PF, Rand TH, Barrett T, *et al*. Accessory cell function of human eosinophils. HLA-DR-dependent, MHC-restricted antigen-presentation and IL-1 alpha expression. *J Immunol* 1993;**150**:2554–62.

249 Devalia JL, Campbell AM, Sapsford RJ, *et al*. Effect of nitrogen dioxide on synthesis of inflammatory cytokines expressed by human bronchial epithelial cells in vitro. *Am J Respir Cell Mol Biol* 1993;**9**:271–8.

250 Dinarello CA, Mier JW. Lymphokines. *N Engl J Med* 1987; **317**:940–5.

251 Turner M, Chantry D, Buchan G, *et al*. Regulation of expression of human IL-1 alpha and IL-1 beta genes. *J Immunol* 1989;**143**:3556–61.

252 Xu WD, Firestein GS, Taetle R, *et al*. Cytokines in chronic inflammatory arthritis. II. Granulocyte-macrophage colony-stimulating factor in rheumatoid synovial effusions. *J Clin Invest* 1989;**83**:876–82.

253 Kern JA, Lamb RJ, Reed JC, *et al*. Dexamethasone inhibition of interleukin 1 beta production by human monocytes: posttranscriptional mechanisms. *J Clin Invest* 1988;**81**: 237–44.

254 Pennington DW, Lopez AR, Thomas PS, *et al*. Dog mastocytoma cells produce transforming growth factor beta 1. *J Clin Invest* 1992;**90**:35–41.

255 Knudsen PJ, Dinarello CA, Strom TB. Prostaglandins posttranscriptionally inhibit monocyte expression of interleukin 1 activity by increasing intracellular cyclic adenosine monophosphate. *J Immunol* 1986;**137**:3189–94.

256 Ray CA, Black RA, Kronheim SR, *et al*. Viral inhibition of inflammation: cowpox virus encodes an inhibitor of the interleukin-1 beta converting enzyme. *Cell* 1992;**69**:597–604.

257 Greenfeder SA, Nunes P, Kwee L, *et al*. Molecular cloning and characterization of a second subunit of the interleukin 1 receptor complex. *J Biol Chem* 1995;**270**:13757–65.

258 McKean DJ, Podzorski RP, Bell MP, *et al*. Murine T helper cell-2 lymphocytes express type I and type II IL-1 receptors, but only the type I receptor mediates costimulatory activity. *J Immunol* 1993;**151**:3500–10.

259 Colotta F, Dower SK, Sims JE, *et al*. The type II 'decoy' receptor: a novel regulatory pathway for interleukin 1. *Immunol Today* 1994;**15**:562–6.

260 Cao Z, Xiong J, Takeuchi M, *et al*. TRAF6 is a signal transducer for interleukin-1. *Nature* 1996;**383**:443–6.

261 Cao Z, Henzel WJ, Gao X. IRAK: a kinase associated with the interleukin-1 receptor. *Science* 1996;**271**:1128–31.

262 Symons JA, Young PR, Duff GW. Soluble type II interleukin 1 (IL-1) receptor binds and blocks processing of IL-1 beta precursor and loses affinity for IL-1 receptor antagonist. *Proc Natl Acad Sci USA* 1995;**92**:1714–8.

263 Mizel SB, Dayer JM, Krane SM, *et al*. Stimulation of rheumatoid synovial cell collagenase and prostaglandin production by partially purified lymphocyte-activating factor (interleukin 1). *Proc Natl Acad Sci USA* 1981;**78**:2474–7.

264 Matsushima K, Yodoi J, Tagaya Y, *et al*. Down-regulation of interleukin 1 (IL 1) receptor expression by IL 1 and fate of internalized 125I-labeled IL 1 beta in a human large granular lymphocyte cell line. *J Immunol* 1986;**137**:3183–8.

265 Bonin PD, Chiou WJ, McGee JE, *et al*. Two signal transduction pathways mediate interleukin-1 receptor expression in Balb/c3T3 fibroblasts. *J Biol Chem* 1990;**265**: 18643–9.

266 Spriggs MK, Lioubin PJ, Slack J, *et al*. Induction of an interleukin-1 receptor (IL-1R) on monocytic cells. Evidence that the receptor is not encoded by a T cell-type IL-1R mRNA. *J Biol Chem* 1990;**265**:22499–505.

267 Bonin PD, Singh JP. Modulation of interleukin-1 receptor expression and interleukin-1 response in fibroblasts by platelet-derived growth factor. *J Biol Chem* 1988;**263**: 11052–5 (published erratum appears in *J Biol Chem* 1989; **264**:4741).

268 Chiou WJ, Bonin PD, Harris PK, *et al*. Platelet-derived growth factor induces interleukin-1 receptor gene expression in Balb/c 3T3 fibroblasts. *J Biol Chem* 1989;**264**: 21442–5.

269 Lacey DL, Erdmann JM. IL-1 and IL-4 modulate IL-1 receptor expression in a murine T cell line. *J Immunol* 1990;**145**:4145–53.

270 Dubois CM, Ruscetti FW, Palaszynski EW, *et al*. Transforming growth factor beta is a potent inhibitor of interleukin 1 (IL-1) receptor expression: proposed mechanism of inhibition of IL-1 action. *J Exp Med* 1990;**172**: 737–44.

271 Stoeck M, Howe RC, Miescher S, *et al*. Effect of transforming growth factor beta on the EL4 thymoma variant EL4/6.1: dissociation of inhibition of proliferation from expression of IL-1 and IL-2 receptors. *Immunobiology* 1990;**181**:13–21.

272 Onozaki K, Matsushima K, Kleinerman ES, *et al*. Role of interleukin 1 in promoting human monocyte-mediated tumor cytotoxicity. *J Immunol* 1985;**135**:314–20.

273 Shirakawa F, Tanaka Y, Eto S, *et al*. Effect of interleukin 1 on the expression of interleukin 2 receptor (Tac antigen) on human natural killer cells and natural killer-like cell line (YT cells). *J Immunol* 1986;**137**:551–6.

274 Shackelford DA, Trowbridge IS. Induction of expression and phosphorylation of the human interleukin 2 receptor by a phorbol diester. *J Biol Chem* 1984;**259**:11706–12.

275 Suzuki T, Cooper MD. Comparison of the expression of IL 2 receptors by human T and B cells: induction by the polyclonal mitogens, phorbol myristate acetate, and anti-mu antibody. *J Immunol* 1985;**134**:3111–9.

276 Emery DW, Rooney JW, Sibley CH. A gamma interferon-unresponsive variant of cell line 70Z/3, IFN-4, can be partially rescued by phorbol myristate acetate. *Mol Cell Biol* 1989;**9**:5231–3.

277 Yamamoto KK, Gonzalez GA, Biggs WH, *et al*. Phosphorylation-induced binding and transcriptional efficacy of nuclear factor CREB. *Nature* 1988;**334**:494–8.

278 Muegge K, Williams TM, Kant J, *et al*. Interleukin-1 costimulatory activity on the interleukin-2 promoter via AP-1. *Science* 1989;**246**:249–51.

279 Kaur P, Saklatvala J. Interleukin 1 and tumour necrosis factor increase phosphorylation of fibroblast proteins. *FEBS Lett* 1988;**241**:6–10.

280 Greenbaum LA, Horowitz JB, Woods A, *et al*. Autocrine growth of CD4+ T cells. Differential effects of IL-1 on helper and inflammatory T cells. *J Immunol* 1988;**140**: 1555–60.

281 Sironi M, Breviario F, Proserpio P, *et al*. IL-1 stimulates IL-6 production in endothelial cells. *J Immunol* 1989;**142**: 549–53.

282 Elias JA, Trinchieri G, Beck JM, *et al*. A synergistic interaction of IL-6 and IL-1 mediates the thymocyte-stimulating activity produced by recombinant IL-1-stimulated fibroblasts. *J Immunol* 1989;**142**:509–14.

283 Helle M, Boeije L, Aarden LA. IL-6 is an intermediate in IL-1-induced thymocyte proliferation. *J Immunol* 1989; **142**:4335–8.

284 Lipsky PE, Thompson PA, Rosenwasser LJ, *et al*. The role of interleukin 1 in human B cell activation: inhibition of B cell proliferation and the generation of immunoglobulin-secreting cells by an antibody against human leukocytic pyrogen. *J Immunol* 1983;**130**:2708–14.

285 Vink A, Coulie PG, Wauters P, *et al*. B cell growth and differentiation activity of interleukin-HP1 and related murine plasmacytoma growth factors. Synergy with interleukin 1. *Eur J Immunol* 1988;**18**:607–12.

286 Paul WE, Ohara J. B-cell stimulatory factor-1/interleukin 4. *Annu Rev Immunol* 1987;**5**:429–59.

287 Schmidt JA, Mizel SB, Cohen D, *et al*. Interleukin 1, a potential regulator of fibroblast proliferation. *J Immunol* 1982;**128**:2177–82.

288 Raines EW, Dower SK, Ross R. Interleukin-1 mitogenic activity for fibroblasts and smooth muscle cells is due to PDGF-AA. *Science* 1989;**243**:393–6.

289 Postlethwaite AE, Lachman LB, Mainardi CL, *et al*. Interleukin 1 stimulation of collagenase production by cultured fibroblasts. *J Exp Med* 1983;**157**:801–6.

290 Dinarello CA, Savage N. Interleukin-1 and its receptor. *Crit Rev Immunol* 1989;**9**:1–20.

291 Pober JS, Gimbrone MA, Jr., Lapierre LA, *et al*. Overlapping patterns of activation of human endothelial cells by interleukin 1, tumor necrosis factor, and immune interferon. *J Immunol* 1986;**137**:1893–6.

292 Godding V, Stark JM, Sedgwick JB, *et al*. Adhesion of activated eosinophils to respiratory epithelial cells is enhanced by tumor necrosis factor-alpha and interleukin-1 beta. *Am J Respir Cell Mol Biol* 1995;**13**:555–62.

293 Bochner BS, Luscinskas FW, Gimbrone MA Jr, *et al*. Adhesion of human basophils, eosinophils, and neutrophils to interleukin 1-activated human vascular endothelial cells: contributions of endothelial cell adhesion molecules. *J Exp Med* 1991;**173**:1553–7.

294 Borish L, Mascali JJ, Dishuck J, *et al*. Detection of alveolar macrophage-derived IL-1 in asthma: inhibition with corticosteroids. *J Immunol* 1992;**149**:3078–82.

295 Sousa AR, Lane SJ, Nakhosteen JA, *et al*. Expression of interleukin-1 beta (IL-1beta) and interleukin-1 receptor antagonist (IL-1ra) on asthmatic bronchial epithelium. *Am J Respir Crit Care Med* 1996;**154**:1061–6.

296 Sousa AR, Trigg CJ, Lane SJ, *et al*. Effect of inhaled glucocorticoids on IL-1 beta and IL-1 receptor antagonist (IL-1ra) expression in asthmatic bronchial epithelium. *Thorax* 1997;**52**:407–10.

297 Tsukagoshi H, Sakamoto T, Xu W, *et al*. Effect of interleukin-1β on airway hyperresponsiveness and inflammation in sensitized and non-sensitized Brown-Norway rats. *J Allergy Clin Immunol* 1994;**93**:464–9.

298 Sanz MJ, Weg VB, Bolanowski MA, *et al*. IL-1 is a potent inducer of eosinophil accummulation in rat skin. *J Immunol* 1995;**154**:1364–73.

299 Koto H, Mak JC, Haddad EB, *et al*. Mechanisms of impaired beta-adrenoceptor-induced airway relaxation by interleukin-1β in vivo in the rat. *J Clin Invest* 1996;**98**: 1780–7.

300 Pang L, Holland E, Knox AJ. Role of cyclooxygenase-2 induction in interleukin-1 β induced attenuation of cultured human airway smooth muscle cells cyclic-AMP generation in response to isoprenaline. *Br J Pharmacol* 1998;**125**:1320–8.

301 Gearing AJ, Beckett P, Christodoulou M, *et al*. Processing of tumour necrosis factor-alpha precursor by metalloproteinases. *Nature* 1994;**370**:555–7.

302 Costa JJ, Matossian K, Resnick MB, *et al*. Human eosinophils can express the cytokines tumor necrosis factor-α and macrophage inflammatory protein-1α. *J Clin Invest* 1993;**91**:2673–84.

303 Devalia JL, Campbell AM, Sapsford RJ, *et al*. Effect of nitrogen dioxide on synthesis of inflammatory cytokines expressed by human bronchial epithelial cells in vitro. *Am J Respir Cell Mol Biol* 1993;**9**:271–8.

304 Nophar Y, Kemper O, Brakebusch C, *et al*. Soluble forms of tumor necrosis factor receptors (TNF-Rs). The cDNA for the type I TNF-R, cloned using amino acid sequence data of its soluble form, encodes both the cell surface and a soluble form of the receptor. *EMBO J* 1990;**9**:3269–78.

305 Galve de Rochemonteix B, Nicod LP, Dayer JM. Tumor necrosis factor soluble receptor 75: the principal receptor form released by human alveolar macrophages and monocytes in the presence of interferon (gamma). *Am J Respir Cell Mol Biol* 1996;**14**:279–87.

306 Rothe M, Sarma V, Dixit VM, *et al*. TRAF2-mediated activation of NF-kappa B by TNF receptor 2 and CD40. *Science* 1995;**269**:1424–7.

307 Mathias S, Dressler KA, Kolesnick RN. Characterization of a ceramide-activated protein kinase: stimulation by tumor necrosis factor alpha. *Proc Natl Acad Sci USA* 1991; **88**:10009–13.

308 Eder J. Tumour necrosis factor alpha and interleukin 1 signalling: do MAPKK kinases connect it all? *Trends Pharmacol Sci* 1997;**18**:319–22.

309 Cromwell O, Hamid Q, Corrigan CJ, *et al*. Expression and generation of interleukin-8, IL-6 and granulocyte colony-stimulating factor by bronchial epithelial cells and enhancement by IL-1β and tumor necrosis factor-α. *Immunology* 1992;**77**:330–7.

310 Kwon OJ, Collins PD, Au B, *et al*. Glucocorticoid inhibition of TNFα-induced IL-8 gene expression in human primary cultured epithelial cells. *Am Rev Respir Dis* 1993;**147**:A752.

311 Berkman N, Robichaud A, Krishnan VL, *et al*. Expression of RANTES in human airway epithelial cells: effect of corticosteroids and interleukin-4, 10 and 13. *Immunology* 1995;**87**:599–603.

312 Thornhill MH, Wellicome SM, Mahiouz DL, *et al*. Tumor necrosis factor combines with IL-4 or IFN-γ to selectively enhance endothelial cell adhesiveness for T cells. The contribution of vascular adhesion molecule-1-dependent and -independent binding mechanisms. *J Immunol* 1991;**146**: 592–8.

313 Rogalsky V, Todorov G, Den T, *et al*. Increase in protein kinase C activity is associated with human fibroblast growth inhibition. *FEBS Lett* 1992;**304**:153–6.

314 Harkonen E, Virtanen I, Linnala A, *et al*. Modulation of fibronectin and tenascin production in human bronchial epithelial cells by inflammatory cytokines in vitro. *Am J Respir Cell Mol Biol* 1995;**13**:109–15.

315 Kips JC, Tavernier JH, Joos GF, *et al*. The potential role of tumour necrosis factor alpha in asthma. *Clin Exp Allergy* 1993;**23**:247–50.

316 Shah A, Church MK, Holgate ST. Tumour necrosis factor alpha: a potential mediator of asthma. *Clin Exp Allergy* 1995;**25**:1038–44.

317 Hirshman CA, Malley A, Downes H. The basenji-greyhound dog model of asthma: reactivity to *Ascaris suum*, citric acid and methacholine. *J Appl Physiol* 1980;**49**:453–7.

318 Ohno I, Ohkawara Y, Yamauchi K, *et al*. Production of tumour necrosis factor with IgE receptor triggering from sensitized lung tissue. *Am J Respir Cell Mol Biol* 1990;**3**: 285–9.

319 Ohkawara Y, Yamauchi K, Tanno Y, *et al*. Human lung mast cells and pulmonary macrophages produce tumor necrosis factor-α in sensitised lung tissue after IgE receptor triggering. *Am J Respir Cell Mol Biol* 1992;**7**:385–92.

320 Ying S, Robinson DS, Varney V, *et al*. TNF-α mRNA expression in allergic inflammation. *Clin Exp Allergy* 1991; **21**:745–50.

321 Cembrzynska-Norvak M, Szklarz E, Inglot AD, *et al*. Elevated release of TNF-α and interferon-gamma by bronchoalveolar leukocytes from patients with bronchial asthma. *Am Rev Respir Dis* 1993;**147**:291–5.

322 Gosset P, Tsicopoulos A, Wallaert B, *et al*. Increased secretion by tumor necrosis factor and interleukin 6 by alveolar macrophages consecutive to the development of the late asthmatic reaction. *J Allergy Clin Immunol* 1991;**88**:561–71.

323 Gosset P, Tsicopoulos A, Wallaert B, *et al*. Tumor necrosis factor α and interleukin-6 production by human mononuclear phagocytes from allergic asthmatics after IgE-dependent stimulation. *Am Rev Respir Dis* 1992;**146**:768–74.

324 Moffatt MF, Cookson WO. Tumour necrosis factor haplotypes and asthma. *Hum Mol Genet* 1997;**6**:551–4.

325 Albuquerque RV, Hayden CM, Palmer LJ, *et al*. Association of polymorphisms within the tumour necrosis factor (TNF) genes and childhood asthma. *Clin Exp Allergy* 1998;**28**:578–84.

326 Kips JC, Tavernier J, Pauwels RA. Tumor necrosis factor causes bronchial hyperresponsiveness in rats. *Am Rev Respir Dis* 1992;**145**:332–6.

327 Yates DH, Barnes PJ, Thomas PS. Tumor necrosis factor α alters human bronchial reactivity and induces inflammatory cell influx. *Am Rev Respir Dis* 1993;**147**:A1011.

328 Mattoli S, Mattoso VL, Soloperto M, *et al*. Cellular and biochemical characteristics of bronchoalveolar lavage fluid in symptomatic nonallergic asthma. *J Allergy Clin Immunol* 1991;**87**:794–802.

329 Elias JA, Wu Y, Zheng T, *et al*. Cytokine- and virus-stimulated airway smooth muscle cells produce IL-11 and other IL-6-type cytokines. *Am J Physiol* 1997;**273**:L648–55.

330 Rochester CL, Ackerman SJ, Zheng T, *et al*. Eosinophil-fibroblast interactions. Granule major basic protein interacts with IL-1 and transforming growth factor-beta in the stimulation of lung fibroblast IL-6-type cytokine production. *J Immunol* 1996;**156**:4449–56.

331 Lacy P, Levi-Schaffer F, Mahmudi-Azer S, *et al*. Intracellular localization of interleukin-6 in eosinophils from atopic asthmatics and effects of interferon gamma. *Blood* 1998;**91**: 2508–16.

332 Akira S, Taga T, Kishimoto T. Interleukin-6 in biology and medicine. *Adv Immunol* 1993;**54**:1–78.

333 Vercelli D, Jabara HH, Arai K, *et al*. Endogenous interleukin 6 plays an obligatory role in interleukin 4-dependent human IgE synthesis. *Eur J Immunol* 1989;**19**: 1419–24.

334 Schindler R, Mancilla J, Endres S, *et al*. Correlations and interactions in the production of interleukin-6 (IL-6), IL-1, and tumor necrosis factor (TNF) in human blood mononuclear cells: IL-6 suppresses IL-1 and TNF. *Blood* 1990;**75**:40–7.

335 Ulich TR, Yin S, Guo K, *et al*. Intratracheal injection of endotoxin and cytokines. II. Interleukin-6 and transforming growth factor beta inhibit acute inflammation. *Am J Pathol* 1991;**138**:1097–101.

336 Ulich TR, Guo KZ, Remick D, *et al*. Endotoxin-induced cytokine gene expression in vivo. III. IL-6 mRNA and serum protein expression and the in vivo hematologic effects of IL-6. *J Immunol* 1991;**146**:2316–23.

337 DiCosmo BF, Geba GP, Picarella D, *et al*. Airway epithelial cell expression of interleukin-6 in transgenic mice. Uncoupling of airway inflammation and bronchial hyperreactivity. *J Clin Invest* 1994;**94**:2028–35.

338 Maier R, Ganu V, Lotz M. Interleukin-11, an inducible cytokine in human articular chondrocytes and synoviocytes, stimulates the production of the tissue inhibitor of metalloproteinases. *J Biol Chem* 1993;**268**:21527–32.

339 Yin T, Miyazawa K, Yang YC. Characterization of interleukin-11 receptor and protein tyrosine phosphorylation induced by interleukin-11 in mouse 3T3-L1 cells. *J Biol Chem* 1992;**267**:8347–51.

340 Yin T, Yasukawa K, Taga T, *et al*. Identification of a 130-kilodalton tyrosine-phosphorylated protein induced by interleukin-11 as JAK2 tyrosine kinase, which associates with gp130 signal transducer. *Exp Hematol* 1994;**22**:467–72.

341 Yin T, Yang YC. Protein tyrosine phosphorylation and activation of primary response genes by interleukin 11 in B9-TY1 cells. *Cell Growth Differ* 1993;**4**:603–9.

342 Hirayama F, Shih JP, Awgulewitsch A, *et al*. Clonal proliferation of murine lymphohemopoietic progenitors in culture. *Proc Natl Acad Sci USA* 1992;**89**:5907–11.

343 Baumann H, Schendel P. Interleukin-11 regulates the hepatic expression of the same plasma protein genes as interleukin-6. *J Biol Chem* 1991;**266**:20424–7.

344 Leng SX, Elias JA. Interleukin-11 inhibits macrophage interleukin-12 production. *J Immunol* 1997;**159**:2161–8.

345 Einarsson O, Geba GP, Zhu Z, *et al*. Interleukin-11: stimulation in vivo and in vitro by respiratory viruses and induction of airways hyperresponsiveness. *J Clin Invest* 1996;**97**: 915–24.

346 Tang W, Geba GP, Zheng T, *et al*. Targeted expression of IL-11 in the murine airway causes lymphocytic inflammation, bronchial remodeling, and airways obstruction. *J Clin Invest* 1996;**98**:2845–53.

347 Kitamura T, Sata N, Arai K, *et al*. Expression cloning of the human IL-3 receptor cDNA reveals a shared subunit for the human IL-3 and GM-CSF receptors. *Cell* 1991;**66**: 1165–74.

348 Kotsimbos AT, Humbert M, Minshall E, *et al*. Upregulation of alpha GM-CSF-receptor in nonatopic asthma but not in atopic asthma. *J Allergy Clin Immunol* 1997;**99**:666–72.

349 Hercus TR, Bagley CJ, Cambareri B, *et al*. Specific human granulocyte-macrophage colony-stimulating factor antagonists. *Proc Natl Acad Sci USA* 1994;**91**:5838–42.

350 Hallsworth MP, Giembycz MA, Barnes PJ, *et al*. Cyclic AMP-elevating agents prolong or inhibit eosinophil survival depending on prior exposure to GM-CSF. *Br J Pharmacol* 1996;**117**:79–86.

351 Silberstein DS, Owen WF, Gasson JC, *et al*. Enhancement of human eosinophil cytotoxicity and leukotriene synthesis by biosynthetic (recombinant) granulocyte-macrophage colony stimulating factor. *J Immunol* 1986;**137**:3290–4.

352 Bussolino F, Wang JM, Defilippi P, *et al*. Granulocyte- and granulocyte-macrophage-colony stimulating factors induce human endothelial cells to migrate and proliferate. *Nature* 1989;**337**:471–3.

353 Sousa AR, Poston RN, Lane SJ, *et al*. Detection of GM-CSF in asthmatic bronchial epithelium and decrease by inhaled corticosteroids. *Am Rev Respir Dis* 1993;**147**: 1557–61.

354 Broide DH, Firestein GS. Endobronchial allergen challenge: demonstration of cellular source of granulocyte macrophage colony-stimulating factor by in situ hybridization. *J Clin Invest* 1991;**88**:1048–53.

355 Brown PA, Crompton GK, Greening AP. Proinflammatory cytokines in acute asthma. *Lancet* 1991;**338**:590–3.

356 Nakamura Y, Ozaki T, Kamgi T, *et al*. Increased granulocyte-macrophage colony-stimulating factor production by mononuclear cells from peripheral blood of patients with bronchial asthma. *Am Rev Respir Dis* 1993;**147**:87–91.

357 Howell CJ, Pujol J-L, Crea AEG, *et al*. Identification of an alveolar macrophage-derived activity in bronchial asthma that enhances leukotriene C4 generation by human eosinophils stimulated by ionophore A23187 as a granulocyte-macrophage colony-stimulating factor. *Am Rev Respir Dis* 1989;**140**:1340–7.

358 Soloperto M, Mattoso VL, Fasoli A, *et al.* A bronchial epithelial cell-derived factor in asthma that promotes eosinophil activation and survival as GM-CSF. *Am J Physiol* 1991;**260**:L530–8.

359 Xing Z, Ohkawara Y, Jordana M, *et al.* Transfer of granulocyte-macrophage colony-stimulating factor gene to rat lung induces eosinophilia, monocytosis, and fibrotic reactions. *J Clin Invest* 1996;**97**:1102–10.

360 Galli SJ, Zsebo KM, Geissler EN. The kit ligand, stem cell factor. *Adv Immunol* 1994;**55**:1–96.

361 Zhang S, Howarth PH, Roche WR. Cytokine production by cell cultures from bronchial subepithelial myofibroblasts. *J Pathol* 1996;**180**:95–101.

362 Kim YK, Nakagawa N, Nakano K, *et al.* Stem cell factor in nasal polyposis and allergic rhinitis: increased expression by structural cells is suppressed by in vivo topical corticosteroids. *J Allergy Clin Immunol* 1997;**100**:389–99.

363 Yuan Q, Austen KF, Friend DS, *et al.* Human peripheral blood eosinophils express a functional c-kit receptor for stem cell factor that stimulates very late antigen 4 (VLA-4)-mediated cell adhesion to fibronectin and vascular cell adhesion molecule 1 (VCAM-1). *J Exp Med* 1997; **186**:313–23.

364 Mitsui H, Furitsu T, Dvorak AM, *et al.* Development of human mast cells from umbilical cord blood cells by recombinant human and murine c-kit ligand. *Proc Natl Acad Sci USA* 1993;**90**:735–9.

365 Valent P, Spanblochl E, Sperr WR, *et al.* Induction of differentiation of human mast cells from bone marrow and peripheral blood mononuclear cells by recombinant human stem cell factor/kit-ligand in long-term culture. *Blood* 1992;**80**:2237–45.

366 Flanagan JG, Chan DC, Leder P. Transmembrane form of the kit ligand growth factor is determined by alternative splicing and is missing in the Sld mutant. *Cell* 1991;**64**: 1025–35.

367 Kirshenbaum AS, Goff JP, Kessler SW, *et al.* Effect of IL-3 and stem cell factor on the appearance of human basophils and mast cells from CD34+ pluripotent progenitor cells. *J Immunol* 1992;**148**:772–7.

368 Kinashi T, Springer TA. Steel factor and c-kit regulate cell-matrix adhesion. *Blood* 1994;**83**:1033–8.

369 Nilsson G, Butterfield JH, Nilsson K, *et al.* Stem cell factor is a chemotactic factor for human mast cells. *J Immunol* 1994;**153**:3717–23.

370 Mekori YA, Oh CK, Metcalfe DD. IL-3-dependent murine mast cells undergo apoptosis on removal of IL-3. Prevention of apoptosis by c-kit ligand. *J Immunol* 1993;**151**:3775–84.

371 Iemura A, Tsai M, Ando A, *et al.* The c-kit ligand, stem cell factor, promotes mast cell survival by suppressing apoptosis. *Am J Pathol* 1994;**144**:321–8.

372 Bischoff SC, Dahinden CA. c-kit ligand: a unique potentiator of mediator release by human lung mast cells. *J Exp Med* 1992;**175**:237–44.

373 Wershil BK, Tsai M, Geissler EN, *et al.* The rat c-kit ligand, stem cell factor, induces c-kit receptor-dependent mouse mast cell activation in vivo. Evidence that signaling through the c-kit receptor can induce expression of cellular function. *J Exp Med* 1992;**175**:245–55.

374 Columbo M, Horowitz EM, Botana LM, *et al.* The human recombinant c-kit receptor ligand, rhSCF, induces mediator release from human cutaneous mast cells and enhances IgE-dependent mediator release from both skin mast cells and peripheral blood basophils. *J Immunol* 1992;**149**:599–608.

375 Gibbs BF, Arm JP, Gibson K, *et al.* Human lung mast cells release small amounts of interleukin-4 and tumour necrosis factor-alpha in response to stimulation by anti-IgE and stem cell factor. *Eur J Pharmacol* 1997;**327**:73–8.

376 Fiorentino DF, Bond MW, Mosmann TR. Two types of mouse helper T cells. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. *J Exp Med* 1989;**170**:2081.

377 Enk AH, Katz SI. Identification and induction of keratinocyte-derived IL10. *J Immunol* 1992;**149**:92–5.

378 Spits H, de Waal Malefyt R. Functional characterization of human IL-10. *Int Arch Allergy Appl Immunol* 1992;**99**:9–15.

379 Berkman N, John M, Roesems G, *et al.* Inhibition of macrophage inflammatory protein-1a by interleukin-10: differential sensitivities in human blood monocytes and alveolar macrophages. *J Immunol* 1995;**155**:4412–8.

380 Liu Y, Wei SH, Ho AS, *et al.* Expression cloning and characterization of a human IL-10 receptor. *J Immunol* 1994;**152**:1821–9.

381 Tan JC, Indelicato SR, Narula SK, *et al.* Characterization of interleukin-10 receptors on human and mouse cells. *J Biol Chem* 1993;**268**:21053–9.

382 Carson WE, Lindemann MJ, Baiocchi R, *et al.* The functional characterization of interleukin-10 receptor expression on human natural killer cells. *Blood* 1995;**85**: 3577–85.

383 Lai CF, Ripperger J, Morella KK, *et al.* Receptors for interleukin (IL)-10 and IL-6-type cytokines use similar signaling mechanisms for inducing transcription through IL-6 response elements. *J Biol Chem* 1996;**271**:13968–75.

384 Wang P, Wu P, Siegel MI, *et al.* Interleukin (IL)-10 inhibits nuclear factor kappa B (NF kappa B) activation in human monocytes. IL-10 and IL-4 suppress cytokine synthesis by different mechanisms. *J Biol Chem* 1995;**270**:9558–63.

385 Fiorentino DF, Zlotnik A, Mossmann TR, *et al.* IL-10 inhibits cytokine production by activated macrophages. *J Immunol* 1991;**147**:3815–22.

386 de Waal Malefyt R, Abrams J, Bennett B, *et al.* Interleukin 10 (IL-10) inhibits cytokine synthesis by human monocytes: an auto regulatory role of IL-10 produced by monocytes. *J Exp Med* 1991;**179**:1209–20.

387 Seitz M, Loetscher P, Dewald B, *et al.* Interleukin-10 differentially regulates cytokine inhibitor and chemokine release from blood mononuclear cells and fibroblasts. *Eur J Immunol* 1995;**25**:1129–32.

388 Malefyt RdM, Haanen J, Spits H, *et al.* Interleukin 10 (IL-10) and viral IL-10 strongly reduce antigen-specific human T cell proliferation by diminishing the antigen-presenting capacity of monocytes via downregulation of class II major histocompatibility complex expression. *J Exp Med* 1991; **174**:915–24.

389 de Waal Malefyt R, Yssel H, Roncarolo MG, *et al.* Interleukin-10. *Curr Opin Immunol* 1992;**4**:314–20.

390 Cunha FQ, Moncada S, Liew FY. Interleukin-10 (IL-10) inhibits the induction of nitric oxide synthase by interferon-gamma in murine macrophages. *Biochem Biophys Res Commun* 1992;**182**:1155–9.

391 Moore KW, O'Garra A, de Waal Malefyt R, *et al.* Interleukin-10. *Annu Rev Immunol* 1993;**11**:165–90.

392 Schandene L, Alonso Vega C, Willems F, *et al.* B7/CD28-dependent IL-5 production by human resting T cells is inhibited by IL-10. *J Immunol* 1994;**152**:4368–74.

393 Jeannin P, Lecoanet S, Delneste Y, *et al.* IgE versus IgG4 production can be differentially regulated by IL-10. *J Immunol* 1998;**160**:3555–61.

394 Thompson-Snipes LA, Dhar V, Bond MW, *et al.* Interleukin 10: a novel stimulatory factor for mast cells and their progenitors. *J Exp Med* 1991;**173**:507–10.

395 Chen WF, Zlotnik A. IL-10: a novel cytotokic T cell differentiation factor. *J Immunol* 1991;**147**:520–34.

396 Lacraz S, Nicod LP, Chicheportiche R, *et al.* IL-10 inhibits metalloproteinase and stimulates TIMP-1 production in human mononuclear phagocytes. *J Clin Invest* 1995;**96**: 2304–10.

397 Borish L, Aarons A, Rumbyrt J, *et al.* Interleukin-10 regulation in normal subjects and patients with asthma. *J Allergy Clin Immunol* 1996;**97**:1288–96.

398 Dugas N, Vouldoukis I, Becherel P, *et al.* Triggering of CD23b antigen by anti-CD23 monoclonal antibodies induces interleukin-10 production by human macrophages. *Eur J Immunol* 1996;**26**:1394–8.

399 Hobbs K, Negri J, Klinnert M, *et al.* Interleukin-10 and transforming growth factor-beta promoter polymorphisms in allergies and asthma. *Am J Respir Crit Care Med* 1998;**158**:1958–62.

400 Mascali JJ, Cvietusa P, Negri J, *et al.* Anti-inflammatory effects of theophylline: modulation of cytokine production. *Ann Allergy Asthma Immunol* 1996;**77**:34–8.

401 Robinson DS, Tsicopoulos A, Meng Q, *et al.* Increased interleukin-10 messenger RNA expression in atopic allergy and asthma. *Am J Respir Cell Mol Biol* 1996;**14**:113–7.

402 Woolley MJ, Woolley KL, Otis J, *et al.* Inhibitory effects of IL-10 on allergen-induced airway inflammation and airway responses in Brown-Norway rats. *Am J Respir Crit Care Med* 1994;**149**:A760.

403 Zuany Amorim C, Creminon C, Nevers MC, *et al.* Modulation by IL-10 of antigen-induced IL-5 generation, and CD4+ T lymphocyte and eosinophil infiltration into the mouse peritoneal cavity. *J Immunol* 1996;**157**:377–84.

404 Zuany Amorim C, Haile S, Leduc D, *et al.* Interleukin-10 inhibits antigen-induced cellular recruitment into the airways of sensitized mice. *J Clin Invest* 1995;**95**:2644–51.

405 Pretolani M, Goldman M. IL-10: a potential therapy for allergic inflammation? *Immunol Today* 1997;**18**:277–80.

406 Chernoff AE, Granowitz EV, Shapiro L, *et al.* A randomized, controlled trial of IL-10 in humans. Inhibition of inflammatory cytokine production and immune responses. *J Immunol* 1995;**154**:5492–9.

407 Arend WP, Joslin FG, Massoni RJ. Effects of immune complexes on production by human monocytes of interleukin 1 or an interleukin 1 inhibitor. *J Immunol* 1985; **134**:3868–75.

408 Arend WP, Joslin FG, Thompson RC, *et al.* An IL-1 inhibitor from human monocytes. production and characterization of biologic properties. *J Immunol* 1989;**143**: 1851–8.

409 Galve de Rochemonteix B, Nicod LP, Junod AF, *et al.* Characterization of a specific 20- to 25-kD interleukin-1 inhibitor from cultured human lung macrophages. *Am J Respir Cell Mol Biol* 1990;**3**:355–61.

410 Balavoine JF, de Rochemonteix B, Williamson K, *et al.* Prostaglandin E2 and collagenase production by fibroblasts and synovial cells is regulated by urine-derived human interleukin 1 and inhibitor(s). *J Clin Invest* 1986;**78**:1120–4.

411 Seckinger P, Kaufmann MT, Dayer JM. An interleukin 1 inhibitor affects both cell-associated interleukin 1-induced T cell proliferation and PGE2/collagenase production by human dermal fibroblasts and synovial cells. *Immunobiology* 1990;**180**:316–27.

412 Barak V, Treves AJ, Yanai P, *et al.* Interleukin 1 inhibitory activity secreted by a human myelomonocytic cell line (M20). *Eur J Immunol* 1986;**16**:1449–52.

413 Seckinger P, Lowenthal JW, Williamson K, *et al.* A urine inhibitor of interleukin 1 activity that blocks ligand binding. *J Immunol* 1987;**139**:1546–9.

414 Arend WP, Welgus HG, Thompson RC, *et al.* Biological properties of recombinant human monocyte-derived interleukin 1 receptor antagonist. *J Clin Invest* 1990;**85**:1694–7.

415 Bienkowski MJ, Eessalu TE, Berger AE, *et al.* Purification and characterization of interleukin 1 receptor level antago-

nist proteins from THP-1 cells. *J Biol Chem* 1990;**265**: 14505–11.

416 Hannum CH, Wilcox CJ, Arend WP, *et al*. Interleukin-1 receptor antagonist activity of a human interleukin-1 inhibitor. *Nature* 1990;**343**:336–40.

417 Monick M, Glazier J, Hunninghake GW. Human alveolar macrophages suppress interleukin-1 (IL-1) activity via the secretion of prostaglandin E2. *Am Rev Respir Dis* 1987;**135**: 72–7.

418 Wewers MD, Rennard SI, Hance AJ, *et al*. Normal human alveolar macrophages obtained by bronchoalveolar lavage have a limited capacity to release interleukin-1. *J Clin Invest* 1984;**74**:2208–18.

419 Giri JG, Newton RC, Horuk R. Identification of soluble interleukin-1 binding protein in cell-free supernatants. Evidence for soluble interleukin-1 receptor. *J Biol Chem* 1990; **265**:17416–9.

420 Muchmore AV, Decker JM. Uromodulin: a unique 85-kilodalton immunosuppressive glycoprotein isolated from urine of pregnant women. *Science* 1985;**229**:479–81.

421 Abbas AK, Williams ME, Burstein HJ, *et al*. Activation and functions of CD4+ T-cell subsets. *Immunol Rev* 1991;**123**: 5–22.

422 Levine SJ, Benfield T, Shelhamer JH. Corticosteroids induce intracellular interleukin-1 receptor antagonist type I expression by a human airway epithelial cell line. *Am J Respir Cell Mol Biol* 1996;**15**:245–51.

423 Watson ML, Smith D, Bourne AD, *et al*. Cytokines contribute to airway dysfunction in antigen-challenged guinea pigs: inhibition of airway hyperreactivity, pulmonary eosinophil accumulation, and tumor necrosis factor generation by pretreatment with an interleukin-1 receptor antagonist. *Am J Respir Cell Mol Biol* 1993;**8**:365–9.

424 Okada S, Inoue H, Yamauchi K, *et al*. Potential role of interleukin-1 in allergen-induced late asthmatic reactions in guinea pigs: suppressive effect of interleukin-1 receptor antagonist on late asthmatic reaction. *J Allergy Clin Immunol* 1995;**95**:1236–45.

425 Romagnani S. Regulation and deregulation of human IgE synthesis. *Immunol Today* 1990;**11**:316–21.

426 Nakajima H, Iwamoto I, Yoshida S. Aerosolized recombinant interferon-gamma prevents antigen-induced eosinophil recruitment in mouse trachea. *Am Rev Respir Dis* 1993;**148**:1102–4.

427 Look DC, Rapp SR, Keller BT, *et al*. Selective induction of intracellular adhesion molecule-1 by interferon-gamma in human airway epithelial cells. *Am J Physiol* 1992;**263**:L79–87.

428 Gifford GE, Lohmann-Matthess ML. Gamma interferon priming of mouse and human macrophages for induction of tumor necrosis factor production by bacterial lipopolysaccharide. *J Natl Cancer Inst* 1987;**78**:121–4.

429 Billiau A, Dijkmans R. Interferon-gamma: mechanism of action and therapeutic potential. *Biochem Pharmacol* 1990; **40**:1433–9.

430 Sen GC, Lenggel P. The interferon system: a bird's eye view of its biochemistry. *J Biol Chem* 1992;**267**:5017–9.

431 Gusella GL, Musso T, Bosco MC, *et al*. IL-2 up-regulates but IFN-γ suppresses IL-8 expression in human monocytes. *J Immunol* 1993;**151**:2725–32.

432 Chomarat P, Rissoan MC, Banchereau J, *et al*. Interferon gamma inhibits interleukin 10 production by monocytes. *J Exp Med* 1993;**177**:523–7.

433 Donnelly RP, Freeman SL, Hayes MP. Inhibition of IL-10 expression by IFN-gamma up-regulates transcription of TNF-alpha in human monocytes. *J Immunol* 1995;**155**: 1420–7.

434 Leonard C, Tormey V, Burke C, *et al*. Allergen-induced cytokine production in atopic disease and its relationship to disease severity. *Am J Respir Cell Mol Biol* 1997;**17**:368–75.

435 Koning H, Neijens HJ, Baert MR, *et al*. T cell subsets and cytokines in allergic and non-allergic children. I. Analysis of IL-4, IFN-gamma and IL-13 mRNA expression and protein production. *Cytokine* 1997;**9**:416–26.

436 Hayden C, Pereira E, Rye P, *et al*. Mutation screening of interferon-gamma (IFNγ) as a candidate gene for asthma. *Clin Exp Allergy* 1997;**27**:1412–6.

437 Lack G, Bradley KL, Hamelmann E, *et al*. Nebulized IFN-gamma inhibits the development of secondary allergic responses in mice. *J Immunol* 1996;**157**:1432–9.

438 Iwamoto I, Nakajima H, Endo H, *et al*. Interferon gamma regulates antigen-induced eosinophil recruitment into the mouse airways by inhibiting the infiltration of CD4+ T cells. *J Exp Med* 1993;**177**:573–6.

439 Li XM, Chopra RK, Chou TY, *et al*. Mucosal IFN gene transfer inhibits allergic responses in mice. *J Immunol* 1996;**157**:3216–9.

440 Coyle AJ, Tsuyuki S, Bertrand C, *et al*. Mice lacking the IFN-gamma receptor have impaired ability to resolve a lung eosinophilic inflammatory response associated with a prolonged capacity of T cells to exhibit a Th2 cytokine profile. *J Immunol* 1996;**156**:2680–5.

441 Zuany Amorim C, Leduc D, Vargaftig BB, *et al*. Modulation by rm interferon-gamma and CD4+ T-lymphocytes of allergic eosinophil accumulation in the mice peritoneal cavity. *Ann NY Acad Sci* 1994;**725**:34–43.

442 Lack G, Nelson HS, Amran D, *et al*. Rush immunotherapy results in allergen-specific alterations in lymphocyte function and interferon-gamma production in CD4+ T cells. *J Allergy Clin Immunol* 1997;**99**:530–8.

443 Durham SR, Till SJ. Immunologic changes associated with allergen immunotherapy. *J Allergy Clin Immunol* 1998;**102**: 157–64.

444 Bentley AM, Hamid Q, Robinson DS, *et al*. Prednisolone treatment in asthma. Reduction in the numbers of eosinophils, T cells, tryptase-only positive mast cells, and modulation of IL-4, IL-5, and interferon-gamma cytokine gene expression within the bronchial mucosa. *Am J Respir Crit Care Med* 1996;**153**:551–6.

445 Boguniewicz M, Martin RJ, Martin D, *et al*. The effects of nebulized recombinant interferon-gamma in asthmatic airways. *J Allergy Clin Immunol* 1995;**95**:133–5.

446 Trinchieri G. Interleukin-12: a proinflammatory cytokine with immunoregulatory functions that bridge innate resistance and antigen-specific adaptive immunity. *Annu Rev Immunol* 1995;**13**:251–6.

447 Macatonia SE, Hosken NA, Litton M, *et al*. Dendritic cells produce IL-12 and direct the development of Th1 cells from naive CD4+ T cells. *J Immunol* 1995;**154**:5071–9.

448 Chua AO, Chizzonite R, Desai BB, *et al*. Expression cloning of a human IL-12 receptor component. A new member of the cytokine receptor superfamily with strong homology to gp130. *J Immunol* 1994;**153**:128–36.

449 Robertson MJ, Soiffer RJ, Wolf SF, *et al*. Responses of human natural killer (NK) cells to NK cell stimulatory factor (NKSF): cytolytic activity and proliferation of NK cells are differentially regulated by NKSF. *J Exp Med* 1992;**175**: 779–85.

450 Gately MK, Desai B, Wolitzky AG, *et al*. Regulation of human lymphocyte proliferation by a heterodimeric cytokine, IL-12 (cytotoxic lymphocyte maturation factor). *J Immunol* 1991;**147**:874–9.

451 Perussia B, Chan SH, D'Andrea A, *et al*. Natural killer (NK) cell stimulatory factor or IL-12 has differential effects on the proliferation of TCR-ab+, TCR-td+ T lymphocytes, and NK cells. *J Immunol* 1992;**149**:3495–9.

452 Bertagnolli MM, Lin B-Y, Young D, *et al*. IL-12 augments antigen-dependent proliferation of activated T lymphocytes. *J Immunol* 1992;**149**:3778–82.

453 Kobayashi M, Fitz L, Ryan M, *et al*. Identification and purification of natural killer cell stimulatory factor (NKSF), a cytokine with multiple biological effects on human lymphocytes. *J Exp Med* 1989;**170**:827–32.

454 Gately MK, Wolitzky AG, Quinn PM, *et al*. Regulation of human cytolytic lymphocyte responses by interleukin-12. *Cell Immunol* 1992;**143**:127–30.

455 Chan SH, Perussia B, Gupta JW, *et al*. Induction of interferon γ production by natural killer cell stimulatory factor: characterization of the responder cells and synergy with other inducers. *J Exp Med* 1991;**173**:869–79.

456 Wolf SF, Temple PA, Koboyashi M, *et al*. Cloning of cDNA for natural killer cell stimulatory factor, a heterodimeric cytokine with multiple biologic effects on T and natural killer cells. *J Immunol* 1991;**146**:3074–9.

457 Schoenhaut DS, Chua AO, Wolitzky AG, *et al*. Cloning and expression of murine IL-12. *J Immunol* 1992;**148**:3433–7.

458 Manetti R, Parronchi P, Giudizi MG, *et al*. Natural killer cell stimulatory factor (interleukin 12 (IL-12)) induces T helper type 1 (Th1)-specific immune responses and inhibits the development of IL-4-producing Th cells. *J Exp Med* 1993;**177**:1199–204.

459 Hsieh C-S, Macatonia SE, Tripp CS, *et al*. Development of T 1 CD4+ T cells through IL-12 produced by Listeria-induced macrophages. *Science* 1993;**260**:547–9.

460 Kiniwa M, Gately M, Gubler U, *et al*. Recombinant interleukin-12 suppresses the synthesis of IgE by interleukin-4 stimulated human lymphocytes. *J Clin Invest* 1992;**90**:262–6.

461 Manetti R, Gerosa F, Giudizi MG, *et al*. Interleukin 12 induces stable priming for interferon gamma (IFN-γ) production during differentiation of human T helper (Th) cells and transient IFN-γ production in established Th2 cell clones. *J Exp Med* 1994;**179**:1273–83.

462 Kips JC, Brusselle GJ, Joos GF, *et al*. Interleukin-12 inhibits antigen-induced airway hyperresponsiveness in mice. *Am J Respir Crit Care Med* 1996;**153**:535–9.

463 Gavett SH, O'Hearn DJ, Li X, *et al*. Interleukin 12 inhibits antigen-induced airway hyperresponsiveness, inflammation, and Th2 cytokine expression in mice. *J Exp Med* 1995;**182**:1527–36.

464 Bruselle GG, Kips JC, Peleman RA, *et al*. Role of IFN-gamma in the inhibition of the allergic airway inflammation caused by IL-12. *Am J Respir Cell Mol Biol* 1997;**17**: 767–71.

465 Sur S, Lam J, Bouchard P, *et al*. Immunomodulatory effects of IL-12 on allergic lung inflammation depend on timing of doses. *J Immunol* 1996;**157**:4173–80.

466 van der Pouw Kraan TC, Boeije LC, de Groot ER, *et al*. Reduced production of IL-12 and IL-12-dependent IFN-gamma release in patients with allergic asthma. *J Immunol* 1997;**158**:5560–5.

467 Hamid QA, Schotman E, Jacobson MR, *et al*. Increases in IL-12 messenger RNA+ cells accompany inhibition of allergen-induced late skin responses after successful grass pollen immunotherapy (see comments). *J Allergy Clin Immunol* 1997;**99**:254–60.

468 van der Pouw Kraan TC, Boeije LC, Smeenk RJ, *et al*. Prostaglandin-E2 is a potent inhibitor of human interleukin 12 production. *J Exp Med* 1995;**181**:775–9.

469 Panina-Bordignon P, Mazzeo D, Lucia PD, *et al*. Beta₂-agonists prevent Th1 development by selective inhibition of interleukin 12. *J Clin Invest* 1997;**100**:1513–9.

470 Luster AD. Chemokines: chemotactic cytokines that mediate inflammation. *N Engl J Med* 1998;**338**:436–45.

471 Wolpe SD, Davatelis G, Sherry B, *et al*. Macrophages secrete a novel heparin-binding protein with inflammatory

and neutrophil chemokinetic properties. *J Exp Med* 1988;**167**:570–81.

472 Obaru K, Fukuda M, Maeda S, *et al*. A cDNA clone used to study mRNA inducible in human tonsillar lymphocytes by a tumor promoter. *J Biochem* 1986;**99**:885–94.

473 Zipfel PF, Balke J, Irving S, *et al*. Mitogenic activation of human T cells induces two closely related genes which share structural similarities with a new family of secreted factors. *J Immunol* 1989;**142**:1582–90.

474 Miller MD, Hata S, de Waal Malefyt R, *et al*. A novel polypeptide secreted by activated human T lymphocytes. *J Immunol* 1989;**143**:2907–16.

475 Lipes MA, Napolitano M, Jeang KT, *et al*. Identification, cloning, and characterization of an immune activation gene. *Proc Natl Acad Sci USA* 1988;**85**:9704–8.

476 Berkman N, Jose P, Williams T, *et al*. Corticosteroid inhibition of macrophage inflammatory protein-1α expression in human monocytes and alveolar macrophages. *Am J Physiol* 1995;**269**:L443–52.

477 Sporn SA, Eierman DF, Johnson CE, *et al*. Monocyte adherence results in selective induction of novel genes sharing homology with mediators of inflammation and tissue repair. *J Immunol* 1990;**144**:4434–41.

478 Miller MD, Krangel MS. Biology and biochemistry of the chemokines: a family of chemotactic and inflammatory cytokines. *Crit Rev Immunol* 1992;**12**:17–46.

479 Yoshimura T, Yuhki N, Moore SK, *et al*. Human monocyte chemoattractant protein-1 (MCP-1). Full-length cDNA cloning, expression in mitogen-stimulated blood mononuclear leukocytes, and sequence similarity to mouse competence gene JE. *FEBS Lett* 1989;**244**:487–93.

480 Matsushima K, Larsen CG, DuBois GC. Purification and characterisation of a novel monocyte chemotactic and activating factor produced by a human myelomonocytic cell line. *J Exp Med* 1989;**169**:1485–90.

481 Schall TJ, Jongstra J, Dyer BJ, *et al*. A human T cell-specific molecule is a member of a new gene family. *J Immunol* 1988;**141**:1018–25.

482 Chang HC, Hsu F, Freeman GJ, *et al*. Cloning and expression of a gamma-interferon-inducible gene in monocytes: a new member of a cytokine gene family. *Int Immunol* 1989;**1**:388–97.

483 Van Damme J, Proost P, Lenaerts J-P, *et al*. Structural and functional identification of two human, tumor-derived monocyte chemotactic proteins (MCP-2 and MCP-3) belonging to the chemokine family. *J Exp Med* 1992;**176**:59–64.

484 Minty A, Chalon P, Guillemot JC, *et al*. Molecular cloning of the MCP-3 chemokine gene and regulation of its expression. *Eur Cytok Network* 1993;**4**:99–104.

485 Opdenakker G, Froyen G, Fiten P, *et al*. Human monocyte chemotactic protein-3 (MCP-3): molecular cloning of the cDNA and comparison with other chemokines. *Biochem Biophys Res Commun* 1993;**191**:535–42.

486 Uguccioni M, Loetscher P, Forssmann U, *et al*. Monocyte chemotactic protein 4 (MCP-4), a novel structural and functional analogue of MCP-3 and eotaxin. *J Exp Med* 1996;**183**:2379–84.

487 Berkhout TA, Sarau HM, Moores K, *et al*. Cloning, in vitro expression, and functional characterization of a novel human CC chemokine of the monocyte chemotactic protein (MCP) family (MCP-4) that binds and signals through the CC chemokine receptor 2B. *J Biol Chem* 1997;**272**:16404–13.

488 Jose PJ, Griffiths-Johnson DA, Collins PD, *et al*. Eotaxin: a potent eosinophil chemoattractant cytokine detected in a guinea pig model of allergic airways inflammation. *J Exp Med* 1994;**179**:881–7.

489 Ponath PD, Qin S, Ringler DJ, *et al*. Cloning of the human eosinophil chemoattractant, eotaxin: expression, receptor binding, and functional properties suggest a mechanism for the selective recruitment of eosinophils. *J Clin Invest* 1996;**97**:604–12.

490 Andrew DP, Chang MS, McNinch J, *et al*. STCP-1 (MDC) CC chemokine acts specifically on chronically activated Th2 lymphocytes and is produced by monocytes on stimulation with Th2 cytokines IL-4 and IL-13. *J Immunol* 1998;**161**:5027–38.

491 Schall TJ, Jongstra J, Dyer BJ, *et al*. A human T cell-specific molecule is a member of a new gene family. *J Immunol* 1992;**141**:1018–25.

492 Miller MD, Wilson SD, Dorf ME, *et al*. Sequence and chromosomal location of the I-309 gene. Relationship to genes encoding a family of inflammatory cytokines. *J Immunol* 1990;**145**:2737–44.

493 Ziegler SF, Tough TW, Franklin TL, *et al*. Induction of macrophage inflammatory protein-1 gene expression in human monocytes by lipopolysaccharide and IL-7. *J Immunol* 1991;**147**:2234–9.

494 Kasama T, Strieter RM, Standiford TJ, *et al*. Expression and regulation of human neutrophil-derived macrophage inflammatory protein 1α. *J Exp Med* 1993;**178**:63–72.

495 Stellato C, Collins P, Ponath PD, *et al*. Production of the novel C-C chemokine MCP-4 by airway cells and comparison of its biological activity to other C-C chemokines. *J Clin Invest* 1997;**99**:926–36.

496 Lilly CM, Nakamura H, Kesselman H, *et al*. Expression of eotaxin by human lung epithelial cells: induction by cytokines and inhibition by glucocorticoids. *J Clin Invest* 1997;**99**:1767–73.

497 Sousa AR, Lane SJ, Nakhosteen JA, *et al*. Increased expression of the monocyte chemoattractant protein-1 in bronchial tissues from asthmatic subjects. *Am J Respir Cell Mol Biol* 1994;**10**:142–7.

498 Izumi S, Hirai K, Miyamasu M, *et al*. Expression and regulation of monocyte chemoattractant protein-1 by human eosinophils. *Eur J Immunol* 1997;**27**:816–24.

499 Ying S, Meng Q, Taborda Barata L, *et al*. Human eosinophils express messenger RNA encoding RANTES and store and release biologically active RANTES protein. *Eur J Immunol* 1996;**26**:70–6.

500 Neote K, Digregorio D, Mak JY, *et al*. Molecular cloning, functional expression and signaling characteristics of a C-C chemokine receptor. *Cell* 1993;**72**:415–25.

501 Gao J-L, Kuhns DB, Tiffany HL, *et al*. Structure and functional expression of the human macrophage inflammatory protein 1α/RANTES receptor. *J Exp Med* 1993;**177**:1421–7.

502 Combadiere C, Ahuja SK, Murphy PM. Cloning and functional expression of a human eosinophil CC chemokine receptor. *J Biol Chem* 1995;**270**:16491–4.

503 Charo IF, Myers SJ, Herman A, *et al*. Molecular cloning and functional expression of two monocyte chemoattractant protein 1 receptors reveals alternative splicing of the carboxyl-terminal tails. *Proc Natl Acad Sci USA* 1994;**91**:2752–6.

504 Ponath PD, Qin S, Post TW, *et al*. Molecular cloning and characterization of a human eotaxin receptor expressed selectively on eosinophils. *J Exp Med* 1996;**183**:2437–48.

505 Power CA, Meyer A, Nemeth K, *et al*. Molecular cloning and functional expression of a novel CC chemokine receptor cDNA from a human basophilic cell line. *J Biol Chem* 1995;**270**:19495–500.

506 Hoogewerf A, Black D, Proudfoot AE, *et al*. Molecular cloning of murine CC CKR-4 and high affinity binding of chemokines to murine and human CC CKR-4. *Biochem Biophys Res Commun* 1996;**218**:337–43.

507 Raport CJ, Gosling J, Schweickart V-LX, *et al*. Molecular cloning and functional characterisation of a novel human CC chemokine receptor (CCR5) for RANTES, MIP-1β and MIP-1α. *J Biol Chem* 1996;**271**:17161–5.

508 Baba M, Imai T, Nishimura M, *et al*. Identification of CCR6, the specific receptor for a novel lymphocyte-directed CC chemokine LARC. *J Biol Chem* 1997;**272**:14893–8.

509 Yoshida R, Imai T, Hieshima K, *et al*. Molecular cloning of a novel human CC chemokine EBI1-ligand chemokine that is a specific functional ligand for EBI1, CCR7. *J Biol Chem* 1997;**272**:13803–9.

510 Roos RS, Loetscher M, Legler DF, *et al*. Identification of CCR8, the receptor for the human CC chemokine I-309. *J Biol Chem* 1997;**272**:17251–4.

511 Ying S, Robinson DS, Meng Q, *et al*. Enhanced expression of eotaxin and CCR3 mRNA and protein in atopic asthma. Association with airway hyperresponsiveness and predominant co-localization of eotaxin mRNA to bronchial epithelial and endothelial cells. *Eur J Immunol* 1997;**27**:3507–16.

512 Heath H, Qin S, Rao P, *et al*. Chemokine receptor usage by human eosinophils. The importance of CCR3 demonstrated using an antagonistic monoclonal antibody. *J Clin Invest* 1997;**99**:178–84.

513 Loetscher P, Seitz M, Baggiolini M, *et al*. Interleukin-2 regulates CC chemokine receptor expression and chemotactic responsiveness in T lymphocytes (see comments). *J Exp Med* 1996;**184**:569–77.

514 Bonecchi R, Bianchi G, Bordignon PP, *et al*. Differential expression of chemokine receptors and chemotactic responsiveness of type 1 T helper cells (Th1s) and Th2s. *J Exp Med* 1998;**187**:129–34.

515 Sallusto F, Mackay CR, Lanzavecchia A. Selective expression of the eotaxin receptor CCR3 by human T helper 2 cells. *Science* 1997;**277**:2005–7.

516 Loetscher P, Uguccioni M, Bordoli L, *et al*. CCR5 is characteristic of Th1 lymphocytes. *Nature* 1998;**391**:344–5.

517 Tanaka Y, Adams TH, Hubschner S, *et al*. T cell adherence induced by proteoglycan-immobilised cytokine macrophage inflammatory protein 1β. *Nature* 1993;**361**:79–82.

518 Rot A, Krieger M, Brunner T, *et al*. RANTES and macrophage inflammatory protein 1 induce the migration and activation of normal human eosinophil granulocytes. *J Exp Med* 1992;**176**:1489–95.

519 Kameyoshi Y, Dorschner A, Mallet A, *et al*. Cytokine RANTES released by thrombin-stimulated platelets is a potent attractant for human eosinophils. *J Exp Med* 1992;**176**:587–92.

520 Alam R, Stafford S, Forsythe P, *et al*. RANTES is a chemotactic and activating factor for human eosinophils. *J Immunol* 1993;**150**:3442–7.

521 Meurer R, Van Riper G, Feeney W, *et al*. Formation of eosinophilic and monocytic intradermal inflammatory sites in the dog by injection of human RANTES but not human monocyte chemoattractant protein 1, human macrophage inflammatory protein 1α, or human interleukin 8. *J Exp Med* 1993;**178**:1913–21.

522 Dahinden CA, Geiser T, Brunner T, *et al*. Monocyte chemotactic protein 3 is a most effective basophil- and eosinophil-activating chemokine. *J Exp Med* 1994;**179**:751–6.

523 Weber M, Uguccioni M, Ochensberger B, *et al*. Monocyte chemotactic protein MCP-2 activates human basophil and eosinophil leukocytes similar to MCP-3. *J Immunol* 1995;**154**:4166–72.

524 Dahinden CA, Geiser T, Brunner T, *et al*. Monocyte chemotactic protein 3 is a most effective basophil- and eosinophil-activating chemokine. *J Exp Med* 1994;**179**:751–6.

525 Hisada T, Hellewell P, Teixeira MM, *et al*. α₄-integrin dependent eotaxin induction of bronchial hyperresponsive-

ness and eosinophil migration in IL-5 transgenic mice. *Am J Respir Cell Mol Biol* 1999 (in press).

526 Burke Gaffney A, Hellewell PG. Eotaxin stimulates eosinophil adhesion to human lung microvascular endothelial cells. *Biochem Biophys Res Commun* 1996;**227**:35–40.

527 Schall T, Bacon K, Toy K, *et al*. Selective attraction of monocytes and T lymphocytes of the memory phenotype by cytokine RANTES. *Nature* 1990;**347**:669–71.

528 Schall TJ, Bacon K, Camp RD, *et al*. Human macrophage inflammatory protein alpha (MIP-1 alpha) and MIP-1 beta chemokines attract distinct populations of lymphocytes. *J Exp Med* 1993;**177**:1821–6.

529 Taub DD, Conlon K, Lloyd AR, *et al*. Preferential migration of activated CD4+ and CD8+ T cells in response to MIP-1α and MIP-1β. *Science* 1993;**260**:355–7.

530 Tanaka Y, Adams DH, Hubscher S, *et al*. T-cell adhesion induced by proteoglycan-immobilized cytokine MIP-1 beta (see comments). *Nature* 1993;**361**:79–82.

531 Loetscher P, Seitz M, Clark Lewis I, *et al*. Monocyte chemotactic proteins MCP-1, MCP-2, and MCP-3 are major attractants for human CD4+ and CD8+ T lymphocytes. *FASEB J* 1994;**8**:1055–60.

532 Carr MW, Roth SJ, Luther E, *et al*. Monocyte chemoattractant protein 1 acts as a T-lymphocyte chemoattractant. *Proc Natl Acad Sci USA* 1994;**91**:3652–6.

533 Loetscher P, Seitz M, Clark Lewis I, *et al*. Activation of NK cells by CC chemokines. Chemotaxis, Ca²⁺ mobilization, and enzyme release. *J Immunol* 1996;**156**:322–7.

534 Maghazachi AA, Al Aarkaty A, Schall TJ. C-C chemokines induce the chemotaxis of NK and IL-2 activated NK cells: role for G proteins. *J Immunol* 1994;**153**:4969–77.

535 Taub DD, Lloyd AR, Conlon K, *et al*. Recombinant human interferon-inducible protein 10 is a chemoattractant for human monocytes and T lymphocytes and promotes T cell adhesion to endothelial cells. *J Exp Med* 1993;**177**:1809–14.

536 Kelner GS, Kennedy J, Bacon KB, *et al*. Lymphotactin: a cytokine that represents a new class of chemokine. *Science* 1994;**266**:1395–9.

537 Kuna P, Reddigari SR, Rucinski D, *et al*. Monocyte chemotactic and activating factor is a potent histamine-releasing factor for human basophils. *J Exp Med* 1992;**175**:489–93.

538 Alam R, Forsythe PA, Lett-Brown MA, *et al*. Interleukin-8 and RANTES inhibit basophil histamine release induced with monocyte chemotactic and activating factor/monocyte chemoattractant peptide-1 and histamine releasing factor. *Am J Respir Cell Mol Biol* 1992;**7**:427–33.

539 Bischoff SC, Krieger M, Brunner T, *et al*. Monocyte chemotactic protein 1 is a potent activator of human basophils. *J Exp Med* 1992;**175**:1271–5.

540 Bischoff SC, Krieger M, Brunner T, *et al*. RANTES and related chemokines activate human basophil granulocytes through different G protein-coupled receptors. *Eur J Immunol* 1993;**23**:761–7.

541 Kuna P, Reddigarl SR, Schall TJ, *et al*. RANTES, a monocyte and T lymphocyte chemotactic cytokine releases histamine from human basophils. *J Immunol* 1992;**149**:636–42.

542 Yoshimura T, Robinson EA, Appela E, *et al*. Three forms of monocyte-derived neutrophil chemotactic factor (MDNCF) distinguished by different lengths of the amino-terminal sequence. *Mol Immunol* 1989;**26**:87–93.

543 Yoshimura T, Robinson EA, Tanaka S, *et al*. Purification and amino acid analysis of two human monocyte chemoattractants produced by phytohemagglutinin-stimulated human blood mononuclear leukocytes. *J Immunol* 1989;**142**:1956–62.

544 Rollins BJ, Walz A, Baggiolini M. Recombinant human MCP-1/JE induces chemotaxis, calcium flux, and the respiratory burst in human monocytes. *Blood* 1991;**78**:1112–6.

545 Sozzani S, Luini W, Molino M, *et al*. The signal transduction pathway involved in the migration induced by a monocyte chemotactic cytokine. *J Immunol* 1991;**147**:2215–21.

546 Miller MD, Krangel MS. The human cytokine I-309 is a monocyte chemoattractant. *Proc Natl Acad Sci USA* 1992;**89**:2950–4.

547 Zachariae CO, Anderson AO, Thompson HL, *et al*. Properties of monocyte chemotactic and activating factor (MCAF) purified from a human fibrosarcoma cell line. *J Exp Med* 1990;**171**:2177–82.

548 Jiang Y, Beller DI, Frendl G, *et al*. Monocyte chemoattractant protein-1 regulates adhesion molecule expression and cytokine production in human monocytes. *J Immunol* 1992;**148**:2423–8.

549 Sozzani S, Luini W, Borsatti A, *et al*. Receptor expression and responsiveness of human dendritic cells to a defined set of CC and CXC chemokines. *J Immunol* 1997;**159**:1993–2000.

550 Alam R, York J, Boyars M, *et al*. Increased MCP-1, RANTES and MIP-1α in bronchoalveolar lavage fluid of allergic asthmatic patients. *Am J Respir Crit Care Med* 1996;**153**:1398–404.

551 Fahy JV, Figueroa DJ, Wong HH, *et al*. Similar RANTES levels in healthy and asthmatic airways by immunoassay and in situ hybridization. *Am J Respir Crit Care Med* 1997;**155**:1095–100.

552 Cruikshank WW, Long A, Tarpy RE, *et al*. Early identification of interleukin-16 (lymphocyte chemoattractant factor) and macrophage inflammatory protein 1 alpha (MIP1 alpha) in bronchoalveolar lavage fluid of antigen-challenged asthmatics. *Am J Respir Cell Mol Biol* 1995;**13**:738–47.

553 Berkman N, Krishnan VL, Gilbey T, *et al*. Expression of RANTES mRNA and protein in airways of patients with mild asthma. *Am J Respir Crit Care Med* 1996;**154**:1804–11.

554 Taguchi M, Sampath D, Koga T, *et al*. Patterns for RANTES secretion and intercellular adhesion molecule 1 expression mediate transepithelial T cell traffic based on analyses in vitro and in vivo. *J Exp Med* 1998;**187**:1927–40.

555 Humbert M, Ying S, Corrigan C, *et al*. Bronchial mucosal expression of the genes encoding chemokines RANTES and MCP-3 in symptomatic atopic and nonatopic asthmatics: relationship to the eosinophil-active cytokines interleukin (IL)-5, granulocyte macrophage-colony-stimulating factor, and IL-3. *Am J Respir Cell Mol Biol* 1997;**16**:1–8.

556 Chihara J, Yasuba H, Tsuda A, *et al*. Elevation of the plasma level of RANTES during asthma attacks. *J Allergy Clin Immunol* 1997;**100**:S52–5.

557 Mattoli S, Stacey MA, Sun G, *et al*. Eotaxin expression and eosinophilic inflammation in asthma. *Biochem Biophys Res Commun* 1997;**236**:299–301.

558 Lamkhioued B, Renzi PM, Abi Younes S, *et al*. Increased expression of eotaxin in bronchoalveolar lavage and airways of asthmatics contributes to the chemotaxis of eosinophils to the site of inflammation. *J Immunol* 1997;**159**:4593–601.

559 Humbles AA, Conroy DM, Marleau S, *et al*. Kinetics of eotaxin generation and its relationship to eosinophil accumulation in allergic airways disease: analysis in a guinea pig model in vivo. *J Exp Med* 1997;**186**:601–12.

560 Brown JR, Kleimberg J, Marini M, *et al*. Kinetics of eotaxin expression and its relationship to eosinophil accumulation and activation in bronchial biopsies and bronchoalveolar lavage (BAL) of asthmatic patients after allergen inhalation. *Clin Exp Immunol* 1998;**114**:137–46.

561 Stafford S, Li H, Forsythe PA, *et al*. Monocyte chemotactic protein-3 (MCP-3)/fibroblast-induced cytokine (FIC) in eosinophilic inflammation of the airways and the inhibitory effects of an anti-MCP-3/FIC antibody. *J Immunol* 1997;**158**:4953–60.

562 Elsner J, Petering H, Hochstetter R, *et al*. The CC chemokine antagonist Met-RANTES inhibits eosinophil effector functions through the chemokine receptors CCR1 and CCR3. *Eur J Immunol* 1997;**27**:2892–8.

563 Walz A, Baggiolini M. Generation of the neutrophil-activating peptide NAP-2 from platelet basic protein or connective tissue-activating peptide III through monocyte proteases. *J Exp Med* 1990;**171**:449–54.

564 Haskill S, Peace A, Morris J, *et al*. Identification of three related human GRO genes encoding cytokine functions. *Proc Natl Acad Sci USA* 1990;**87**:7732–6.

565 Geiser T, Dewald B, Ehrengruber MU, *et al*. The interleukin-8-related chemotactic cytokines GRO alpha, GRO beta, and GRO gamma activate human neutrophil and basophil leukocytes. *J Biol Chem* 1993;**268**:15419–24.

566 Walz A, Burgener R, Car B, *et al*. Structure and neutrophil-activating properties of a novel inflammatory peptide (ENA-78) with homology to interleukin 8. *J Exp Med* 1991;**174**:1355–62.

567 Proost P, De Wolf-Peeters C, Conings R, *et al*. Identification of a novel granulocyte chemotactic protein (GCP-2) from human tumor cells. In vitro and in vivo comparison with natural forms of GRO, IP-10, and IL-8. *J Immunol* 1993;**150**:1000–10.

568 Wolpe SD, Cerami A. Macrophage inflammatory proteins 1 and 2: members of a novel superfamily of cytokines. *FASEB J* 1989;**3**:2565–73.

569 Kasahara K, Strieter RM, Chensue SW, *et al*. Mononuclear cell adherence induces neutrophil chemotactic factor/interleukin-8 gene expression. *J Leuk Biol* 1991;**50**:287–95.

570 Metinko AP, Kunkel SL, Standiford TJ, *et al*. Anoxia-hyperoxia induces monocyte-derived interleukin-8. *J Clin Invest* 1992;**90**:791–8.

571 Braun RK, Franchini M, Erard F, *et al*. Human peripheral blood eosinophils produce and release interleukin-8 on stimulation with calcium ionophore. *Eur J Immunol* 1993;**23**:956–60.

572 Galy AH, Spits H. IL-1, IL-4, and IFN-gamma differentially regulate cytokine production and cell surface molecule expression in cultured human thymic epithelial cells. *J Immunol* 1991;**147**:3823–30.

573 Elner VM, Strieter RM, Elner SG, *et al*. Neutrophil chemotactic factor (IL-8) gene expression by cytokine-treated retinal pigment epithelial cells. *Am J Pathol* 1990;**136**:745–50.

574 Standiford TJ, Kunkel SL, Basha MA, *et al*. Interleukin-8 gene expression by a pulmonary epithelial cell line. A model for cytokine networks in the lung. *J Clin Invest* 1990;**86**:1945–53.

575 Kwon O, Au BT, Collins PD, *et al*. Tumour necrosis factor-induced interleukin-8 expression in pulmonary cultured human airway epithelial cells. *Am J Physiol* 1994;**267**:L398–405.

576 Choi AMK, Jacoby DB. Influenza virus A infection induces interleukin-8 gene expression in human airway epithelial cells. *FEBS Lett* 1992;**309**:327–9.

577 Nakamura H, Yoshimura K, McElvaney NG, *et al*. Neutrophil elastase in respiratory epithelial lining fluid of individuals with cystic fibrosis induces interleukin-8 gene expression in a human bronchial epithelial cell line. *J Clin Invest* 1992;**89**:1478–84.

578 Mukaida N, Shiroo M, Matsushima K. Genomic structure of the human monocyte-derived neutrophil chemotactic factor IL-8. *J Immunol* 1989;**143**:1366–71.

579 Mukaida N, Mahé Y, Matsushima K. Cooperative interaction of nuclear factor κB and cis-regulatory enhancer binding protein-like factor bonding elements in activating the interleukin-8 gene by pro-inflammatory cytokines. *J Biol Chem* 1990;**265**:21128–33.

580 Sica A, Matsushima K, Van Damme J, *et al*. IL-1 transcriptionally activates the neutrophil chemotactic factor/IL-8 gene in endothelial cells. *Immunology* 1990;**69**:548–53.

581 Mukaida N, Matsushima K. Regulation of IL-8 production and the characteristics of the receptor for IL-8. *Cytokine* 1992;**4**:41–53.

582 Mukaida N, Harada A, Yasumoto K, *et al*. Properties of pro-inflammatory cell type-specific leukocyte chemotactic cytokines, interleukin 8 (IL-8) and monocyte chemotactic and activating factor (MCAF). *Microbiol Immunol* 1992;**36**:773–89.

583 Holmes WE, Lee J, Kuang WJ, *et al*. Structure and functional expression of a human interleukin 8 receptor. *Science* 1991;**253**:1278–80.

584 Murphy PM, Tiffany HL. Cloning of complementary DNA encoding a functional human interleukin-8 receptor. *Science* 1991;**253**:1280–3.

585 Loetscher M, Loetscher P, Brass N, *et al*. Lymphocyte-specific chemokine receptor CXCR3: regulation, chemokine binding and gene localization. *Eur J Immunol* 1998;**28**:3696–705.

586 Cole KE, Strick CA, Paradis TJ, *et al*. Interferon-inducible T cell alpha chemoattractant (I-TAC): a novel non-ELR CXC chemokine with potent activity on activated T cells through selective high affinity binding to CXCR3. *J Exp Med* 1998;**187**:2009–21.

587 Kupper RW, Dewald B, Jakobs KH, *et al*. G-protein activation by interleukin 8 and related cytokines in human neutrophil plasma membranes. *Biochem J* 1992;**282**:429–34.

588 Lee J, Horuk R, Rice GC, *et al*. Characterization of two high affinity human interleukin-8 receptors. *J Biol Chem* 1992;**267**:16283–7.

589 Baggiolini M, Wymann MP. Turning on the respiratory burst. *Trends Biochem Sci* 1990;**15**:69–72.

590 Detmers PA, Lo SK, Olsen-Egbert E, *et al*. Neutrophil-activating protein 1/interleukin 8 stimulates the binding activity of the leukocyte adhesion receptor CD11b/CD18 on human neutrophils. *J Exp Med* 1990;**171**:1155–62.

591 Detmers PA, Powell DE, Walz A, *et al*. Differential effects of neutrophil-activating peptide 1/IL-8 and its homologues on leukocyte adhesion and phagocytosis. *J Immunol* 1991;**147**:4211–7.

592 Schroder JM. The monocyte-derived neutrophil activating peptide (NAP/interleukin 8) stimulates human neutrophil arachidonate-5-lipoxygenase, but not the release of cellular arachidonate. *J Exp Med* 1989;**170**:847–63.

593 Bussolino F, Sironi M, Bocchietto E, *et al*. Synthesis of platelet-activating factor by polymorphonuclear neutrophils stimulated with interleukin-8. *J Biol Chem* 1992;**267**:14598–603.

594 Kernen P, Wymann MP, von Tscharner V, *et al*. Shape changes, exocytosis, and cytosolic free calcium changes in stimulated human eosinophils. *J Clin Invest* 1991;**87**:2012–7.

595 Bacon KB, Camp RD. Interleukin (IL)-8-induced in vitro human lymphocyte migration is inhibited by cholera and pertussis toxins and inhibitors of protein kinase C. *Biochem Biophys Res Commun* 1990;**169**:1099–104.

596 Leonard EJ, Yoshimura T, Tanaka S, *et al*. Neutrophil recruitment by intradermally injected neutrophil attractant/activation protein-1. *J Invest Dermatol* 1991;**96**:690–4.

597 Swensson O, Schubert C, Christophers E, *et al*. Inflammatory properties of neutrophil-activating protein-1/interleukin 8 (NAP-1/IL-8) in human skin: a light- and electronmicroscopic study. *J Invest Dermatol* 1991;**96**:682–9.

598 Dahinden CA, Kurimoto Y, De Weck AL, *et al*. The neutrophil-activating peptide NAF/NAP-1 induces histamine and leukotriene release by interleukin 3-primed basophils. *J Exp Med* 1989;**170**:1787–92.

599 White MV, Yoshimura T, Hook W, *et al*. Neutrophil attractant/activation protein-1 (NAP-1) causes human basophil histamine release. *Immunol Lett* 1989;**22**:151–4.

600 Bischoff SC, Baggiolini M, De Weck AL, *et al*. Interleukin 8-inhibitor and inducer of histamine and leukotriene release in human basophils. *Biochem Biophys Res Commun* 1991;**179**:628–33.

601 Walz A, Meloni F, Clark-Lewis I, *et al*. [Ca^{2+}]$_i$ changes and respiratory burst in human neutrophils and monocytes induced by NAP-1/interleukin-8, NAP-2, and gro/MGSA. *J Leuk Biol* 1991;**50**:279–86.

602 Marini M, Vittori E, Hollemburg J, *et al*. Expression of the potent inflammatory cytokines granulocyte-macrophage colony stimulating factor, interleukin-6 and interleukin-8 in bronchial epithelial cells of patients with asthma. *J Allergy Clin Immunol* 1992;**82**:1001–9.

603 Shute JK, Vrugt B, Lindley IJ, *et al*. Free and complexed interleukin-8 in blood and bronchial mucosa in asthma. *Am J Respir Crit Care Med* 1997;**155**:1877–83.

604 Teran LM, Carroll MP, Frew AJ, *et al*. Leukocyte recruitment after local endobronchial allergen challenge in asthma. Relationship to procedure and to airway interleukin-8 release. *Am J Respir Crit Care Med* 1996;**154**:469–76.

605 Agrawal KP. Specific airway conductance in guinea pigs: normal values and histamine induced fall. *Respir Physiol* 1981;**43**:23–30.

606 Keatings VM, Collins PD, Scott DM, *et al*. Differences in interleukin-8 and tumor necrosis factor-α in induced sputum from patients with chronic obstructive pulmonary disease or asthma. *Am J Respir Crit Care Med* 1996;**153**:530–4.

607 Chanez P, Enander I, Jones I, *et al*. Interleukin 8 in bronchoalveolar lavage of asthmatic and chronic bronchitis patients. *Int Arch Allergy Immunol* 1996;**111**:83–8.

608 Warringa RA, Koenderman L, Kok PT, *et al*. Modulation and induction of eosinophil chemotaxis by granulocyte-macrophage colony-stimulating factor and interleukin-3. *Blood* 1991;**77**:2694–700.

609 Collins PD, Weg VB, Faccioli LH, *et al*. Eosinophil accumulation induced by human interleukin-8 in the guinea-pig in vivo. *Immunology* 1993;**79**:312–8.

610 Douglass JA, Dhami D, Gurr CE, *et al*. Influence of interleukin-8 challenge in the nasal mucosa in atopic and nonatopic subjects. *Am J Respir Crit Care Med* 1994;**150**:1108–13.

611 Bywater M, Rorsman F, Bongcam Rudloff E, *et al*. Expression of recombinant platelet-derived growth factor A- and B-chain homodimers in rat-1 cells and human fibroblasts reveals differences in protein processing and autocrine effects. *Mol Cell Biol* 1988;**8**:2753–62.

612 Ostman A, Rall L, Hammacher A, *et al*. Synthesis and assembly of a functionally active recombinant platelet-derived growth factor AB heterodimer. *J Biol Chem* 1988;**263**:16202–8.

613 Raines EW, Ross R. Platelet-derived growth factor. I. High yield purification and evidence for multiple forms. *J Biol Chem* 1982;**257**:5154–60.

614 Deuel TF, Huang JS, Proffitt RT, *et al*. Human platelet-derived growth factor. Purification and resolution into two active protein fractions. *J Biol Chem* 1981;**256**:8896–9.

615 Hammacher A, Hellman U, Johnsson A, *et al*. A major part of platelet-derived growth factor purified from human platelets is a heterodimer of one A and one B chain. *J Biol Chem* 1988;**263**:16493–8.

616 Hart CE, Bailey M, Curtis DA, *et al*. Purification of PDGF-AB and PDGF-BB from human platelet extracts and identification of all three PDGF dimers in human platelets. *Biochemistry* 1990;**29**:166–72.

617 Sejersen T, Betsholtz C, Sjolund M, *et al*. Rat skeletal myoblasts and arterial smooth muscle cells express the gene for the A chain but not the gene for the B chain (c-sis) of platelet-derived growth factor (PDGF) and produce a PDGF-like protein. *Proc Natl Acad Sci USA* 1986;**83**:6844–8.

618 Yarden Y, Escobedo JA, Kuang WJ, *et al*. Structure of the receptor for platelet-derived growth factor helps define a family of closely related growth factor receptors. *Nature* 1986;**323**:226–32.

619 Gronwald RG, Grant FJ, Haldeman BA, *et al*. Cloning and expression of a cDNA coding for the human platelet-derived growth factor receptor: evidence for more than one receptor class. *Proc Natl Acad Sci USA* 1988;**85**:3435–9.

620 Hart CE, Forstrom JW, Kelly JD, *et al*. Two classes of PDGF receptor recognize different isoforms of PDGF. *Science* 1988;**240**:1529–31.

621 Matsui T, Heidaran M, Miki T, *et al*. Isolation of a novel receptor cDNA establishes the existence of two PDGF receptor genes. *Science* 1989;**243**:800–4.

622 Heldin CH. Structural and functional studies on platelet-derived growth factor. *EMBO J* 1992;**11**:4251–9.

623 Seifert RA, Hart CE, Phillips PE, *et al*. Two different subunits associate to create isoform-specific platelet-derived growth factor receptors. *J Biol Chem* 1989;**264**:8771–8.

624 Westermark B, Claesson Welsh L, Heldin CH. Structural and functional aspects of the receptors for platelet-derived growth factor. *Prog Growth Factor Res* 1989;**1**:253–66.

625 Bryckaert MC, Lindroth M, Lonn A, *et al*. Transforming growth factor (TGFβ) decreases the proliferation of human bone marrow fibroblasts by inhibiting the platelet-derived growth factor (PDGF) binding. *Exp Cell Res* 1988;**179**:311–21.

626 Ishikawa O, LeRoy EC, Trojanowska M. Mitogenic effect of transforming growth factor beta 1 on human fibroblasts involves the induction of platelet-derived growth factor alpha receptors. *J Cell Physiol* 1990;**145**:181–6.

627 Bonner JC, Badgett A, Lindroos PM, *et al*. Basic fibroblast growth factor induces expression of the PDGF receptor-alpha on human bronchial smooth muscle cells. *Am J Physiol* 1996;**271**:L880–8.

628 Larsson O, Latham C, Zickert P, *et al*. Cell cycle regulation of human diploid fibroblasts: possible mechanisms of platelet-derived growth factor. *J Cell Physiol* 1989;**139**:477–83.

629 Greenberg ME, Hermanowski AL, Ziff EB. Effect of protein synthesis inhibitors on growth factor activation of c-fos, c-myc, and actin gene transcription. *Mol Cell Biol* 1986;**6**:1050–7.

630 Hall DJ, Brownlee C, Stiles CD. Interleukin-1 is a potent regulator of JE and KC gene expression in quiescent BALB/c fibroblasts. *J Cell Physiol* 1989;**141**:154–9.

631 Rose R, Raines EW, Bowen-Pope DF. The biology of platelet-derived growth factor. *Cell* 1986;**46**:155–69.

632 Hirst SJ, Barnes PJ, Twort CHC. PDGF isoform-induced proliferation and receptor expression in human cultured airway smooth muscle cells. *Am J Physiol* 1996;**270**:415–28.

633 Seppa H, Grotendorst G, Seppa S, *et al*. Platelet-derived growth factor in chemotactic for fibroblasts. *J Cell Biol* 1982;**92**:584–8.

634 Grotendorst GR, Seppa HE, Kleinman HK, *et al*. Attachment of smooth muscle cells to collagen and their migration toward platelet-derived growth factor. *Proc Natl Acad Sci USA* 1981;**78**:3669–72.

635 Clark RA, Folkvord JM, Hart CE, *et al*. Platelet isoforms of platelet-derived growth factor stimulate fibroblasts to contract collagen matrices. *J Clin Invest* 1989;**84**:1036–40.

636 Chanez P, Vignola M, Stenger R, *et al*. Platelet-derived growth factor in asthma. *Allergy* 1995;**50**:878–83.

637 Hoshino M, Nakamura Y, Sim J, *et al*. Bronchial subepithelial fibrosis and expression of matrix metalloproteinase-9 in asthmatic airway inflammation. *J Allergy Clin Immunol* 1998;**102**:783–8.

638 Aubert J-D, Hayashi S, Hards J, *et al*. Platelet-derived growth factor and its receptor in lungs from patients with asthma and chronic airflow obstruction. *Am J Physiol* 1994;**266**:L655–63.

639 Ohno I, Nitta Y, Yamauchi K, *et al*. Eosinophils as a potential source of platelet-derived growth factor B-chain (PDGF-B) in nasal polyposis and bronchial asthma. *Am J Respir Cell Mol Biol* 1995;**13**:639–47.

640 Assoian RK, Fleurdelys BE, Stevenson HC, *et al*. Expression and secretion of type beta transforming growth factor by activated human macrophages. *Proc Natl Acad Sci USA* 1987;**84**:6020–4.

641 Limper AH, Broekelmann TJ, Colby TV, *et al*. Analysis of local mRNA expression for extracellular matrix proteins and growth factors using in situ hybridization in fibroproliferative lung disorders. *Chest* 1991;**99**:55–6S.

642 Khalil N, Bereznay O, Sporn M, *et al*. Macrophage production of transforming growth factor beta and fibroblast collagen synthesis in chronic pulmonary inflammation. *J Exp Med* 1989;**170**:727–37.

643 Kelley J, Fabisiak JP, Hawes K, *et al*. Cytokine signalling in lung: transforming growth factor-β secretion by lung fibroblasts. *Am J Physiol* 1991;**260**:L123–8.

644 Ohno I, Lea RG, Flanders KC, *et al*. Eosinophils in chronologically inflamed human upper airway tissues express transforming growth factor β1 gene. *J Clin Invest* 1992;**89**:1662–8.

645 Elovic A, Wong DT, Weller PF, *et al*. Expression of transforming growth factors-alpha and beta 1 messenger RNA and product by eosinophils in nasal polyps. *J Allergy Clin Immunol* 1994;**93**:864–9.

646 Grotendorst GR, Smale G, Pencev D. Production of transforming growth factor beta by human peripheral blood monocytes and neutrophils. *J Cell Physiol* 1989;**140**:396–402.

647 Sacco O, Romberger D, Rizzino A, *et al*. Spontaneous production of transforming growth factor-β2 by primary cultures of bronchial epithelial cells. *J Clin Invest* 1992;**90**:1379–85.

648 Yamauchi K, Martinet Y, Basset P, *et al*. High levels of transforming growth factor-β are present in the epithelial cell lining fluid of the normal human lower respiratory tract. *Am Rev Respir Dis* 1988;**137**:1360–3.

649 Aubert J-D, Dalal BI, Bai TR, *et al*. Transforming growth factor β gene expression in human airways. *Thorax* 1994;**45**:225–32.

650 Wang XF, Lin HY, Ng Eaton E, *et al*. Expression cloning and characterization of the TGF-beta type III receptor. *Cell* 1991;**67**:797–805.

651 Moses HL, Yang EL, Pietenpol JA. TGFβ stimulation and inhibition of cell proliferation: new mechanistic insights. *Cell* 1990;**63**:245–7.

652 Ignotz JBC, Ignotz RA, Massagne J. Transforming growth factor-beta stimulates expression of fibronectin and collagen and their incorporation into the extracellular matrix. *J Biol Chem* 1986;**261**:4337–45.

653 Infeld MD, Brennan JA, Davis PB. Human tracheobronchial epithelial cells direct migration of lung fibroblasts in three-dimensional collagen gels. *Am J Physiol* 1992;**262**:L535–41.

654 Masui T, Wakefield L, Lechner J, *et al*. Type B transforming growth factor is the primary differentiation-inducing serum factor for normal human bronchial epithelial cells. *Proc Natl Acad Sci USA* 1986;**83**:2438–42.

655 Raghu G, Masta S, Meyers D, *et al*. Collagen synthesis by normal and fibrotic human lung fibroblasts and the effect of transforming growth factor β. *Am Rev Respir Dis* 1989;**140**:95–100.

656 Wahl SM, Hunt DA, Wakefield LM, *et al*. Transforming growth factor type beta induces monocyte chemotaxis and growth factor production. *Proc Natl Acad Sci USA* 1987;**84**:5788–92.

657 Gruber BL, Marchese MJ, Kew RR. Transforming growth factor-beta 1 mediates mast cell chemotaxis. *J Immunol* 1994;**152**:5860–7.

658 Kehrl JH, Wakefield LM, Roberts AB, *et al*. Production of transforming growth factor beta by human T lymphocytes and its potential role in the regulation of T cell growth. *J Exp Med* 1986;**163**:1037–50.

659 Cohen MD, Ciocca V, Panettieri RA Jr. TGF-beta 1 modulates human airway smooth-muscle cell proliferation induced by mitogens. *Am J Respir Cell Mol Biol* 1997;**16**:85–90.

660 Black PN, Young PG, Skinner SJ. Response of airway smooth muscle cells to TGF-beta 1: effects on growth and synthesis of glycosaminoglycans. *Am J Physiol* 1996;**271**:L910–7.

661 Minshall EM, Leung DYM, Martin RJ, *et al*. Eosinophil-associated TGFβ1 mRNA expression and airways fibrosis in asthma. *Am J Respir Cell Mol Biol* 1997;**17**:326–33.

662 Chu HW, Halliday JL, Martin RJ, *et al*. Collagen deposition in large airways may not differentiate severe asthma from milder forms of the disease. *Am J Respir Crit Care Med* 1998;**158**:1936–44.

663 Vignola AM, Chanez P, Chiappara G, *et al*. Transforming growth factor-beta expression in mucosal biopsies in asthma and chronic bronchitis. *Am J Respir Crit Care Med* 1997;**156**:591–9.

664 Redington AE, Madden J, Frew AJ, *et al*. Transforming growth factor-beta 1 in asthma. Measurement in bronchoalveolar lavage fluid. *Am J Respir Crit Care Med* 1997;**156**:642–7.

665 Basilico C, Moscatelli D. The FGF family of growth factors and oncogenes. *Adv Cancer Res* 1992;**59**:115–65.

666 Folkman J, Klagsbrun M. Vascular physiology. A family of angiogenic peptides. *Nature* 1987;**329**:671–2.

667 Mignatti P, Tsuboi R, Robbins E, *et al*. In vitro angiogenesis on the human amniotic membrane: requirement for basic fibroblast growth factor-induced proteinases. *J Cell Biol* 1989;**108**:671–82.

668 Moscatelli D, Presta M, Joseph Silverstein J, *et al*. Both normal and tumor cells produce basic fibroblast growth factor. *J Cell Physiol* 1986;**129**:273–6.

669 Presta M, Moscatelli D, Joseph Silverstein J, *et al*. Purification from a human hepatoma cell line of a basic fibroblast growth factor-like molecule that stimulates capillary endothelial cell plasminogen activator production, DNA synthesis, and migration. *Mol Cell Biol* 1986;**6**:4060–6.

670 Jeanny JC, Fayein N, Moenner M, *et al*. Specific fixation of bovine brain and retinal acidic and basic fibroblast growth factors to mouse embryonic eye basement membranes. *Exp Cell Res* 1987;**171**:63–75.

671 Cordon Cardo C, Vlodavsky I, Haimovitz Friedman A, *et al*. Expression of basic fibroblast growth factor in normal human tissues. *Lab Invest* 1990;**63**:832–40.

672 Kelley J. Cytokines of the lung. *Am Rev Respir Dis* 1990;**141**:765–88.

673 Panettieri RA Jr, Goldie RG, Rigby PJ, *et al*. Endothelin-1-induced potentiation of human airway smooth muscle proliferation: an ETA receptor-mediated phenomenon. *Br J Pharmacol* 1996;**118**:191–7.

674 Cambrey AD, Kwon OJ, McAnulty RJ, *et al*. Release of fibroblast proliferative activity from cultured human airway epithelial cells: a role for insulin-like growth factor 1 (IGF-1). *Clin Sci* 1995;**89**:611–8.

675 Noveral JP, Bhala A, Hintz RL, *et al*. Insulin-like growth factor axis in airway smooth muscle cells. *Am J Physiol* 1994;**267**:L761–5.

676 Cohen P, Noveral JP, Bhala A, *et al*. Leukotriene D4 facilitates airway smooth muscle cell proliferation via modulation of the IGF axis. *Am J Physiol* 1995;**269**:L151–7.

677 Kelleher MD, Abe MK, Chao TS, *et al*. Role of MAP kinase activation in bovine tracheal smooth muscle mitogenesis. *Am J Physiol* 1995;**268**:L894–901.

678 Hoshino M, Nakamura Y, Sim JJ. Expression of growth factors and remodelling of the airway wall in bronchial asthma. *Thorax* 1998;**53**:21–7.

679 Hoshino M, Nakamura Y, Sim JJ, *et al*. Inhaled corticosteroid reduced lamina reticularis of the basement membrane by modulation of insulin-like growth factor (IGF)-I expression in bronchial asthma. *Clin Exp Allergy* 1998;**28**:568–77.

680 Chung KF. The role of new asthma treatments. *Allergol Int* 1998;**47**:237–46.