Cytokines in asthma

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Cytokines in asthma. J.C. Kips. ©ERS Journals Ltd 2001.
ABSTRACT: The airway inflammation underlying asthma is regulated by a network of mutually interacting cytokines. The exact functional role of each individual cytokine in the pathogenesis of the disease remains to be fully established.

Type 2 T-helper cells are currently considered to play a crucial role in this process. *In vivo* **animal data suggest a sequential involvement of interleukin (IL)-4 and IL-5 in the induction of allergen-induced airway changes. The potential role of other type 2 T-helper cell-like cytokines in asthma is increasingly being recognized. In particular, IL-4 and -13 display a large degree of redundancy. Whereas IL-4 seems to be crucial in the primary allergen sensitization process, IL-13 might be more important during secondary exposure to aerosolized allergen. Animal models also indicate that T-cell-derived cytokine production, rather than eosinophil influx or immunoglobulin-E synthesis, is causally related to altered airway behaviour.**

An important aspect when evaluating the functional role of cytokines in a complex disease such as asthma is the interaction with other cytokines in the microenvironment. Increased expression of pro-inflammatory cytokines such as tumour necrosis factor-α can further enhance the inflammatory process, and is increasingly linked to disease severity. In addition, decreased expression of immunoregulatory cytokines, including interleukin-12, interleukin-18 or interferon gamma could also strengthen the type 2 T-helper cell-driven inflammatory process.
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Asthma is currently considered and defined as a chronic inflammatory disorder of the airway mucosa [1]. The pathogenesis of the disease process can be regarded as a two-step phenomenon. The first step consists of sensitization to an aeroallergen, which involves the preferential development of antigen-specific T-helper (Th) cells type 2. The second step, which does not occur in all atopic individuals, consists of targeting the Th2-driven allergic inflammation to the lower airways. This inflammatory process is orchestrated and regulated by a complex network of mutually interacting cytokines and growth factors, secreted not only by a range of inflammatory cells but also from structural tissue components, including epithelial cells, fibroblasts and smooth muscle cells. The resulting inflammation of the airway mucosa shows signs of an acute as well as a more chronic type of inflammation [2]. This latter phenomenon causes remodelling of the airway wall, resulting in a number of structural alterations. Biopsy studies in asthma illustrate increased expression of an ever-increasing number of cytokines. Overall, these can be grouped as Th2-like cytokines, such as interleukin (IL)-4, -5, -9 and -13, pro-inflammatory cytokines including tumour necrosis factor-α (TNF-α) and IL-1β, chemokines such as regulated on activation, normal T-cell expressed and secreted (RANTES), eotaxin and monocyte chemotactic protein(MCP)-1, and growth factors, including transforming growth factor-β and epidermal growth factor (fig. 1).

Although insight into the pathophysiology of asthma has increased substantially over recent years, a number of issues remain to be further clarified. These include a better understanding of the exact functional role of each cytokine in the sensitization process and in the complex relationship between inflammation, remodelling and altered airway behaviour. Providing proof of the functional importance of a given cytokine in asthma usually follows Koch′s postulates. This means assessing whether expression of a given cytokine is altered in asthmatic airways, whether exogenous administration of the cytokine mimics certain features of asthma and, finally, whether antagonizing the endogenously released cytokine blocks allergen-induced changes or offers clinical efficacy in ongoing asthma. The data currently available in this respect rely largely on a combination of descriptive human data and interventional studies conducted in *in vivo* animal models. It can be anticipated that further insight into the functional role of cytokines will result in novel therapeutic perspectives. For some cytokines, specific inhibitors are currently being developed for human use. It will be interesting to see how they lead to better understanding of the disease process in the individual patient and allow for fine-tuning of treatment regimens. This review, rather than attempting to cover all
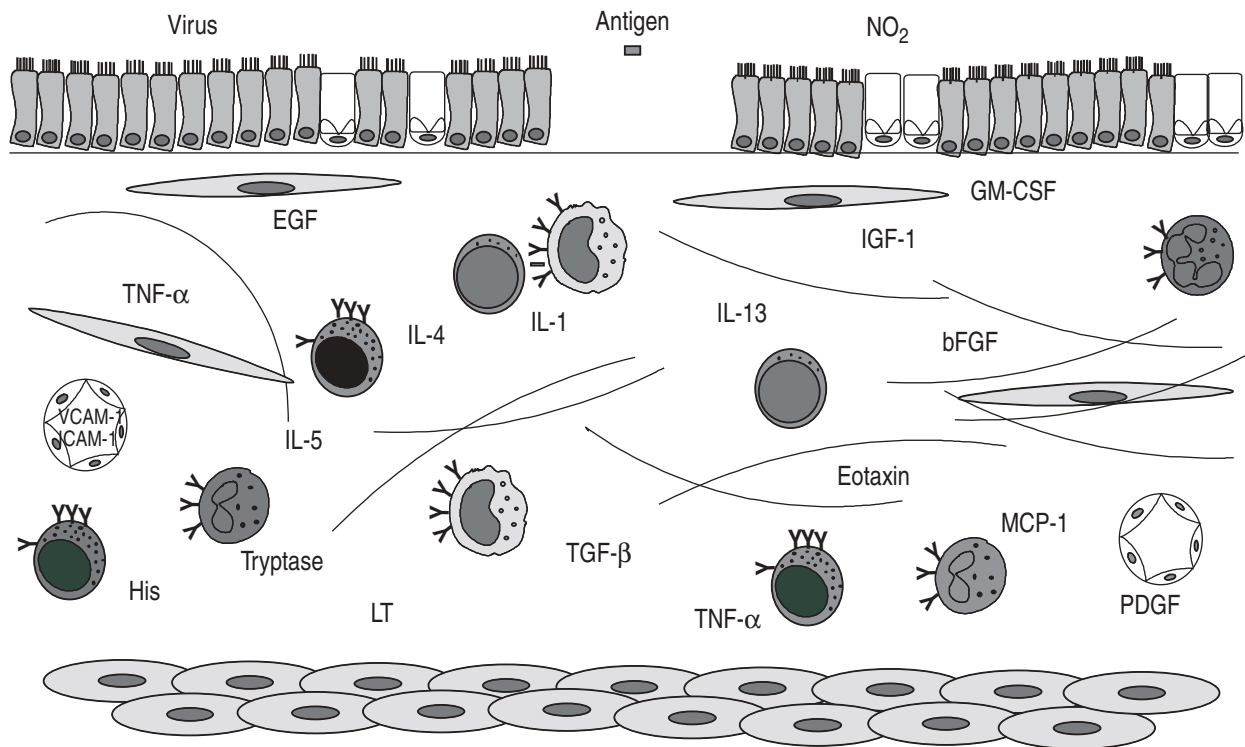
Fig. 1. – Airway inflammation and remodelling in asthma. Schematic section through airway wall. EGF: epidermal growth factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; TNF-α: tumour necrosis-α factor; IL: interleukin; bFGF: basic fibroblast growth factor; VCAM-1: vascular cell adhesion molecule-1; ICAM-1: intercellular adhesion molecule-1; MCP-1: monocyte chemotactic protein-1; His: histamine; LT: leukotriene; TFG-β: transforming growth factor-β; PDGF: platelet-derived growth factor.

cytokines, focuses on a few that have been highlighted as potential therapeutic targets.

Type 2 T-helper cell-like cytokines

Within the range of cytokines produced by Th2, IL-4 and -5 have received considerable interest to date.

Interleukin-4

IL-4 demonstrates a broad range of biological activities. In general terms, it can be described as the main cytokine involved in the pathogenesis of allergic responses, at the same time downregulating acute inflammatory changes [3]. Additional effects that seem of particular importance for asthma include stimulation of mucus-producing cells and fibroblasts, thus also implicating IL-4 in the pathogenesis of airway remodelling [4–6]. Inhalation of recombinant human IL-4 has been shown to induce airway eosinophilia and to cause some degree of bronchial hyperresponsiveness in atopic asthmatics [7]. In addition, bronchial biopsy studies have confirmed increased expression of IL-4 at both the messenger ribonucleic acid (mRNA) and protein level in the airway mucosa of atopic and even nonatopic asthmatics compared to nonasthmatic controls [8–10]. IL-4 exerts its biological activities through binding to the IL-4 receptor (IL-4R), which is expressed on the surface of diverse cell types. The IL-4R

is a heterodimer, consisting of the IL-4-binding IL-4Rα chain and a second chain, which is either the γc chain (shared in common with the receptor for IL-2, -7, -9 and -15) or the IL-13Rα chain [11, 12]. Increased expression of the IL-4Rα chain in the epithelium and subepithelium of asthmatic airways has been reported [13]. Polymorphisms of the IL-4 and IL-4Rα genes have also been related to asthma severity. In particular, the IL-4-589T allele, which has been associated with increased IL-4 gene expression, has been found to be a risk factor for life-threatening asthma [14].

The functional role of IL-4 has been evaluated in a number of *in vivo* animal models. The present author has developed a model of allergen (ovalbumin)-induced airway changes in C57Bl/6 mice. In this model, IL-4 was shown to be essential for the development of ovalbumin-induced eosinophil influx into the airways, immunoglobulin-E (IgE) production and the increase in airway responsiveness [15]. More recent studies show very similar results in mice deficient in signal transducer and activator of transcription (Stat)-6, which is considered central to the signalling pathway for mediating the biological responses to IL-4 [16, 17]. In the present authors' model, mast cell-deficient mice still develop airway eosinophilia in response to ovalbumin exposure, whereas major histocompatibility complex class II-deficient mice, lacking functionally active T-cells, do not [18]. This indicates, as has been confirmed by others, that the crucial role of IL-4 lies in its effect on Th2 development, rather than on the induction of

IgE synthesis and subsequent mast cell degranulation [19]. This is in line with a number of other investigations. TAKEDA et al. [20], for example, have shown that mast cell-deficient mice and their wild-type littermates develop a comparable increase in both airway eosinophil number and bronchial responsiveness when sensitized and exposed to ovalbumin. Similarly, MEHLHOP et al. [21] reported that, in IgE$^{-/-}$ mice, sensitization and exposure to Aspergillus extract induced a comparable degree of airway inflammation and methacholine responsiveness to that found in wild-type animals. Finally, using B-cell-deficient mice, it was shown that the absence of any immunoglobulin production does not prevent development of allergic airway inflammation [22, 23]. Overall, these observations indicate that the IgE/mast cell axis does not play a major role in the induction of allergen-induced airway inflammation and bronchial hyperresponsiveness. Importantly, these experiments do not permit the exclusion of a possible modulatory role of IgE by enhancing T-/B-cell interaction [24, 25].

At the same time, what clearly emerges is the central role of T-cells in these models. Further studies, using different approaches, including pretreatment with anti-CD4 antibodies and passive transfer of cells, confirm the functional importance of CD4 cells and, more specifically, Th2 [26–30]. Importantly, although exogenous administration or lung-specific overexpression of IL-4 in transgenic mice causes epithelial hypertrophy and some degree of peribronchial inflammatory change, this is not accompanied by increased airway hyperresponsiveness, suggesting that IL-4 in itself is insufficient to induce all the changes characteristic of asthma, and that other Th2-derived cytokines are also involved [31, 32]. An obvious possibility in this respect is IL-5.

Interleukin-5

It barely needs repeating that the eosinophil is considered a key effector cell in the pathogenesis of allergic inflammation. Despite possible redundancy with other cytokines, such as IL-3 and granulocyte-macrophage colony-stimulating factor (GMCSF), IL-5 seems to be the primary cytokine involved in vivo in the production, differentiation, maturation and activation of eosinophils [33]. This has been illustrated by several lines of investigation. Exogenous IL-5 administration has been shown to cause eosinophilia in a variety of in vivo models [34]. IL-5-expressing transgenic mice develop lifelong eosinophilia, whereas GM-CSF-expressing transgenic mice show increased numbers of mononuclear cells and neutrophils, but only a minimal increase in the number of eosinophils [35, 36]. Similar findings emerge from knockout mice. For example, the eosinophil inflammatory response to thioglycollate is not abrogated in GM-CSF$^{-/-}$ mice [37]. IL-5$^{-/-}$ mice, on the other hand, show decreased numbers of circulating eosinophils and fail to mount a normal eosinophilic response to parasitic infections or to ovalbumin challenge [38, 39]. It should be pointed out that, even in IL-5$^{-/-}$ mice, a small number of morphologically normal eosinophils remain detectable in the blood. A minor contribution of constitutively expressed IL-3 and GM-CSF to the production of eosinophils can, therefore, not be excluded. However, it is of interest to note that, in the absence of IL-5, local injection of CC chemokines such as eotaxin cannot induce tissue eosinophilia, even if donor eosinophils have been administered to restore or increase the circulating pool, a procedure which in wild-type animals clearly enhances the tissue response to eotaxin [40].

Inhalation of IL-5 has also been shown to increase the percentage of eosinophils in induced sputum and to augment airway hyperresponsiveness in asthma [7]. Again, expression of IL-5 at the mRNA and protein level is increased in the mucosa of asthmatic airways [41, 42]. Expression of IL-5 mRNA has even been shown to correlate with clinical indices of disease severity. This corresponds with other studies, showing that expression of the IL-5R in bronchial biopsy samples is, in >90%, restricted to eosinophils, and that expression of the transmembrane form of the IL-5Rα chain inversely correlates with the baseline forced expiratory volume in one second (FEV1), whereas expression of the soluble IL-5Rα which has IL-5 antagonistic properties, correlates positively with FEV1 [43].

Animal models illustrate that ovalbumin sensitization and exposure in IL-5$^{-/-}$ mice does not cause bronchial hyperresponsiveness as opposed to what is found in wild-type mice [39]. In subsequent studies, it was shown that passive transfer of IL-5-secreting CD4+ T-cells from ovalbumin-sensitized wild-type mice to nonsensitized IL5$^{-/-}$ mice led to airway eosinophilia and an increase in airway responsiveness when these animals were exposed to aerosolized ovalbumin [28]. Similarly, reconstituting IL-5 or IL-5 production, but not IgE, in IL-4$^{-/-}$ mice restored all the allergen-induced airway changes [44]. Again, this supports the concept that IL-4 and IL-5 are sequentially involved in the pathogenesis of allergic airway changes, whereas the role of IgE in the induction of the process seems rather limited. However, it should be noted that experiments using other antigen sources or mouse strains have shown that, although IL-5 is crucial for inducing eosinophil infiltration in the airways, modulation of airway responsiveness can occur independently of IL-5 and airway eosinophilia [30, 45–47]. These observations do not contradict the postulated crucial role of Th2 in this phenomenon. Indeed, other Th2 cytokines can also influence airway responsiveness. For example, COHN et al. [29] reported, using an ovalbumin T-cell receptor transgenic model, that passive transfer of Th2 from IL-4$^{-/-}$ mice can induce airway hyperresponsiveness and pulmonary eosinophil infiltration upon ovalbumin exposure in recipient mice. The passively-transferred T-cells not only produced high levels of IL-5 but also IL-10, and especially IL-13.

Interleukin-13

IL-13 is also present in increased amounts in asthmatic airways, and has very similar biological

Table 1. – Biological properties of interleukin (IL)-13 relevant to asthma

Large overlap with IL-4, but human T-cells have no functional IL-13 receptor
Isotype switching of B-cells to immunoglobulin-E synthesis
Upregulation of $Fc_\varepsilon R_{II}$ expression
Downregulation of production of pro-inflammatory cytokines (TNF-α and IL-1β), chemokines (RANTES) and IL-12
Upregulation of expression of VCAM-1, but not of ICAM-1
Increase in eosinophil survival
Chemotaxis and activation of fibroblasts
Stimulation of mucus production

$Fc_\varepsilon R_{II}$: low-affinity immunoglobulin E receptor; TNF-α: tumour necrosis factor-α; RANTES: regulated on activation, normal T-cell expressed and secreted; VCAM-1: vascular cell adhesion molecule-1; ICAM-1: intercellular adhesion molecule-1.

Table 2. – Biological properties of interleukin (IL)-9 relevant to asthma

Stimulates proliferation of activated T-cells
Enhances immunoglobulin-E production
Upregulates the α chain of the $Fc_\varepsilon R_I$ receptor
Enhances IL-5 receptor expression, and differentiation and survival of eosinophils
Promotes proliferation and differentiation of mast cells
Induces CC chemokine expression in lung epithelial cells

Interleukin-9

Another cytokine derived mainly from Th2, but also from eosinophils, is IL-9 [58]. *In vitro* data indicate that amongst other features, it stimulates proliferation of activated T-cells, enhances production of IgE from B-cells, promotes proliferation and differentiation of mast cells, upregulates the α-chain of the $Fc_\varepsilon R_I$ receptor and induces CC-chemokine expression in lung epithelial cells (table 2). As such, it could, again, contribute substantially to allergen-induced airway changes. Human data show increased expression of IL-9 in bronchial biopsy samples of asthmatics [59]. In addition, genetic analyses have linked IL-9 to bronchial hyperresponsiveness as a major characteristic of asthma. Animal data are slightly less clear regarding the *in vivo* role of IL-9. The lung-specific overexpression in transgenic mice has been shown to induce airway hyperresponsiveness in addition to morphological changes that bear similarities to asthma [60]. However, experiments in IL-9$^{-/-}$ mice indicate that, although IL-9 might play a role in goblet cell hyperplasia and mast cell development, it has little or no effect on eosinophils, T-cell development or immunoglobulin response [61].

The overall message emerging from these and other experiments is that T-cells can alter airway responsiveness in their own right, most probably through production of a cytokine cocktail, the composition of which can vary according to experimental conditions.

Chemokines

Recruitment of inflammatory cells into the airway mucosa requires, in conjunction with the immunoregulatory activity of Th2, expression of adhesion molecules on vascular endothelium and chemokine activity. An abundance of chemokines and chemokine receptors has been identified. Based on the number and position of cysteine residues within their amino acid sequence, chemokines can be categorized as C, CC, CXC or CX3C. The global biological activity of the various cytokines within each structurally related group is largely similar. The CXC or α-chemokines principally attract neutrophils and have, therefore, mainly been related to acute inflammatory processes. To date, models of allergic inflammation have predominantly focused on the CC or β-chemokine family, as these express chemotactic activity towards eosinophils as well as dendritic cells, T-lymphocytes, basophils and monocytes [62]. The precise functional role of each chemokine within this group remains to

activities to IL-4 (table 1) [48–50]. This is reflected in the structure of their receptors. The IL-13R consists of the IL-13Rα1 or α2 chain, which binds IL-13, and the IL-4Rα chain, shared in common with the IL-4R [51]. The signal transduction pathways common to both receptors involve the intracytoplasmatic domain of both chains and are largely STAT-6-dependent. IL-4 can bind to both receptors through IL-4Rα, and IL-13 binds only to its own receptor. With the exception of T-cells, which do not carry functional IL-13Rs, most cell types respond similarly to IL-4 and IL-13 [52]. Because of this large degree of redundancy, it is difficult to establish with certainty the exact role of IL-4 relative to IL-13 in allergen-induced airway changes, but it would appear that both are functionally active. It has been hypothesized that, although IL-4 is crucial for the initial Th2 development during primary sensitization, IL-13 release might prove more important during secondary antigen exposure [11, 53]. This concept is illustrated in a number of *in vivo* animal models. As previously explained, the induction of allergen-induced Th2 development and related phenomena, such as IgE synthesis, airway eosinophilia and airway hyperresponsiveness, is totally abrogated in IL-4$^{-/-}$ mice [15, 19]. The same applies to STAT-6$^{-/-}$ [16, 17] or IL-4R$\alpha^{-/-}$ [54], but not IL-13$^{-/-}$ mice [55]. Administration of neutralizing anti-IL-4 antibodies during sensitization exhibits similar inhibitory effects on Th2 development, thus confirming the importance of IL-4 during the early response to antigen. However, when given only during secondary antigen presentation in already sensitized animals, anti-IL-4 is far less effective in reducing Th2 cytokine production, eosinophil influx and bronchial hyperresponsiveness [19], whereas anti-IL4R maintains therapeutic effects [31]. This confirms *in vitro* data showing that once T-cells have been committed to a Th2-type phenotype, they become IL-4 independent [56]. At the same time, this suggests that, during secondary antigen exposure, IL-13 plays a more important role than IL-4. In line with these observations, neutralizing endogenously released IL-13 with an IL-13Rα2Fc fusion protein during secondary antigen exposure largely inhibits the characteristics of asthma in murine models [54, 57].

be fully explored. A sequential role for different chemokines in antigen-induced eosinophil recruitment has been suggested [63, 64]. Of particular interest for allergic disorders is the observation that CCR3 receptor expression is limited to eosinophils, basophils and Th2. Several CC chemokines bind to the CCR3 receptor, including RANTES, MCP-3, MCP-4 and the CCR3-specific ligand eotaxin. Increased expression of eotaxin and the CCR3 receptor have been described in bronchial mucosa from asthmatics [65]. Eotaxin expression was shown to correlate with the degree of bronchial hyperresponsiveness. In addition, plasma eotaxin levels have been associated with impaired lung function in a large cohort of asthmatics [66]. These various observations have raised interest in the CCR3 receptor as a potential therapeutic target [67]. Blockade of the CCR3 receptor, using either monoclonal antibodies or modified RANTES proteins such as Met-RANTES or AOP-RANTES, has proven effective in *in vivo* animal models [63, 68].

Pro-inflammatory cytokines

Another group of cytokines that needs to be considered are the pro-inflammatory cytokines such as TNF-α and IL-1β. The pleiotropic activities of TNF-α include pro-inflammatory effects such as leukocyte recruitment through upregulation of adhesion molecules on vascular endothelial cells and induction of cytokine and chemokine synthesis [69]. In addition, TNF-α also has the potential to stimulate mesenchymal cells such as fibroblasts or smooth muscle cells, and therefore could play an important role in the pathogenesis of airway remodelling [70, 71]. Elevated levels of TNF-α have been detected in sputum, bronchoalveolar lavage fluid and biopsy samples from asthmatics [72–74]. Inhalation of TNF-α causes airway hyperresponsiveness and an increase in sputum neutrophil counts in healthy volunteers [75]. Genetic analysis also links TNF-α to characteristics of asthma as an association has been described between the -308 TNF-α promoter polymorphism and the degree of bronchial hyperresponsiveness. Allele 2 of the -308 TNF-α polymorphism is characterized by increased releasability of TNF-α in response to various stimuli [76]. Moreover, there is evidence to suggest that TNF-α is an important element in determining the severity of asthma. Sputum and biopsy samples from patients with severe persistent asthma have been shown to contain increased numbers of neutrophils [77–79]. One of the major stimuli for neutrophil recruitment is exposure to endotoxin. The severity of asthma symptoms has been related to the endotoxin content of house dust, rather than to the allergen load in these samples [80]. That the endotoxin-induced effects are largely mediated through the endogenous release of TNF-α is illustrated in *in vivo* animal models. Exogenous administration of TNF-α was shown to induce airway neutrophilia and hyperresponsiveness, whereas pretreatment with anti-TNF-α antibodies profoundly reduced the endotoxin-induced airway changes [81].

Acute asthma attacks might also be largely TNF-α driven. Increased neutrophilia has been reported in sputum from patients who experience an acute asthma attack [82]. Similarly, bronchoalveolar lavage fluid from subjects who require ventilation due to status asthmaticus contain increased numbers of neutrophils and levels of pro-inflammatory cytokines including TNF-α [83].

Immunomodulatory cytokines

When evaluating the functional role of cytokines in asthma, it is important to bear in mind that they act within a network of mutually interacting cytokines. Allergic airway inflammation might, therefore, be induced by not only increased expression of Th2 cytokines but also decreased expression of counteracting ones. Interesting cytokines in this respect include IL-12, IL-18, interferon gamma (IFN-γ) and IL-10 (fig. 2).

Interleukin-12, interleukin-18 and interferon gamma

IL-12 expression has been shown to be reduced in bronchial biopsy samples from asthmatic individuals [49]. IL-12 is produced by antigen-presenting cells and is known to play an important role in Th1/Th2 differentiation during primary antigen presentation [84]. The major antigen presenting cell involved in the process of sensitization to aeroallergens is the dendritic cell present in the airway epithelium. Mucosal dendritic cells demonstrate high antigen uptake but low antigen-presenting capacity. During migration from the airway mucosa to the local lymph nodes, antigen-laden dendritic cells mature, acquiring their full immunostimulatory phenotype. In the lymph nodes, naive T-cells are stimulated and differentiate towards a Th1- or Th2- like phenotype. One of the factors that influence T-cell differentiation is the cytokine composition of the microenvironment, IL-12 having been identified as the necessary cofactor for Th1 development. *In vivo* animal models have confirmed that exogenous administration of IL-12 during the primary sensitization process, suppresses
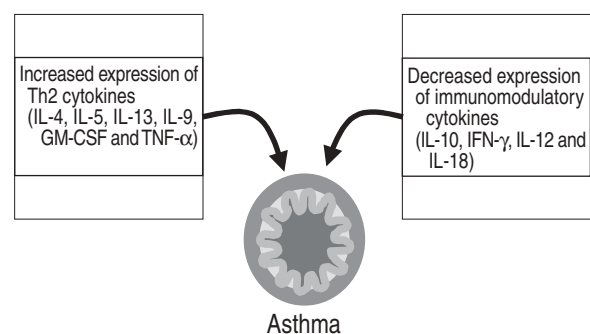

Fig. 2. – The cytokine network involved in the pathogenesis of asthma. Normal airway morphology is shown. Th2: type 2 T-helper cell; IL: interleukin; GM-CSF: granulocyte-macrophage colony-stimulating factor; TNF-α: tumour necrosis factor-α; IFN-γ: interferon gamma.

allergen-induced Th2 development, favouring Th1 differentiation [85, 86].

Interestingly however, even when only administered during secondary antigen exposure, IL-12 retains the capacity to inhibit allergen-induced eosinophilia and airway hyperresponsiveness, despite the persistence of circulating IgE [85]. The precise mechanisms underlying this effect are largely unknown. Fully committed Th2 have been shown to loose their IL-12 responsiveness [87]. Therefore, a reversal of a Th2 towards a Th1 phenotype at this stage is unlikely. IL-12 is known to induce the production of IFN-γ and to downregulate IL-5 production, possibly through endogenous release of IL-10 [88, 89]. However, it has been shown that IL-12 retains its immunomodulatory effect, even when given during secondary antigen presentation in IFN-γR$^{-/-}$ or IL-10$^{-/-}$ mice [90, 91]. The exact mechanisms of these IL-12-mediated effects, therefore, need to be further established.

In view of its biological activities, IL-12 has attracted considerable interest as a potential treatment for allergic disorders. Implementing this approach is, however, hampered by the toxicity of IL-12, which has been noted in human cancer studies [92]. In a recently reported antigen-challenge study in mild asthma, IL-12 was given systemically in incremental doses, as advocated to reduce toxicity. Nevertheless, significant side-effects occurred. In addition, despite a substantial reduction in circulating blood eosinophil count, IL-12 did not influence the antigen-induced early or late asthmatic response [93]. It remains to be further investigated whether topical application or repeated administration of lower doses might prove to be a better therapeutic option. Interesting in this respect is the potential synergistic activity of IL-12 and IL-18. IL-18 is secreted by macrophages and was initially described as IFN-γ-releasing factor [94]. The absence of endogenous IL-18$^{-/-}$ enhances antigen-induced airway eosinophilia [95]. Importantly, IL-12 and IL-18 appear to act synergistically in inducing IFN-γ and in inhibiting IL-4-dependent IgE synthesis as well as inhibiting allergen-induced airway hyperresponsiveness [96]. Whether the combination of both cytokines carries less toxic side-effects than equieffective doses of either cytokine given alone needs to be further evaluated.

In *in vivo* animal models, IFN-γ has also been shown to prevent the development of antigen-induced airway eosinophilia and hyperresponsiveness [97–99]. Similarly, IFN-γR$^{-/-}$ mice develop a prolonged airway eosinophilia in response to allergen [100]. To date, however, exogenous administration of IFN-γ in humans has proven disappointing. Nebulized IFN-γ was reported not to influence baseline FEV1 in mild asthma, and subcutaneous administration of IFN-γ did not offer any improvement in steroid-dependent asthmatics [101, 102].

Interleukin-10

IL-10 is a pleiotropic cytokine that has the potential to downregulate both Th1- and Th2- driven inflammatory processes [103]. It is of interest that IL-10

might also have a beneficial effect on airway remodelling, as it has been shown to reduce collagen type I synthesis and vascular smooth muscle proliferation [104, 105]. The precise functional role of IL-10, however, appears to be somewhat unclear. Whether IL-10 expression is changed in asthma is uncertain, as in some studies reduced and in others increased bronchoalveolar lavage fluid levels were found [106–108]. IL-10, administered exogenously at the time of secondary antigen presentation, reduces antigen-induced airway eosinophilia in animal models [109–111], whereas airway eosinophilia and total serum IgE levels are increased in sensitized IL-10 knockout mice [112, 113]. However, the effects of IL-10 on airway responsiveness are somewhat more contradictory. In some studies, endogenous production of IL-10 was shown to dampen airway responsiveness [113], whereas others have shown that IL-10 enhances the allergen-induced increase in airway responsiveness, despite the reduction in eosinophil recruitment [111, 112].

Conclusion

Type 2 T-helper lymphocytes are presently considered to be the main orchestrator of the allergic airway inflammation underlying asthma. Functional analysis of the role of cytokines, largely based on *in vivo* animal models, confirms this hypothesis. T-cells themselves seem to be the main factor in determining the degree of airway inflammation and hyperresponsiveness (fig. 3). It would appear that cytokine production, rather than the influx of eosinophils or production of immunoglobulin-E, is the cause of bronchial hyperresponsiveness. Importantly, biopsy studies clearly illustrate the presence of a complex cytokine network in asthmatic airways. The redundancy of and the mutual interaction between the cytokines within this network needs to be borne in mind when trying to assess the functional role of an
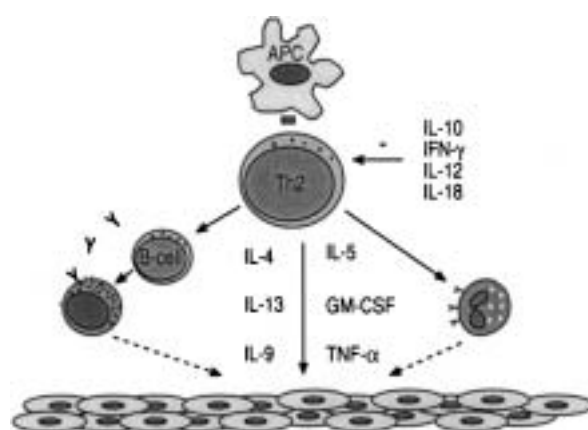

Fig. 3. – The functional role of cytokines involved in the pathogenesis of asthma. APC: antigen-presenting cell; Th2: type 2 T-helper cell; IL: interleukin; IFN-γ: interferon gamma; GM-CSF: granulocyte-macrophage colony-stimulating factor; TNF-α: tumour necrosis factor-α.

individual cytokine in a complex disease process such as asthma.

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