

REVIEW

Cytokines and cytokine receptors in allergic rhinitis: how do they relate to the Th2 hypothesis in allergy?

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Introduction

Allergic rhinitis is thought to result from a series of cellular interactions, starting with allergen-uptake and processing by antigen-presenting cells. These cells present allergen peptides to type-2 T helper (Th2) cells, which in turn induce release of IgE from B-cells. Subsequent allergen binding to IgE on the surface of mast cells results in the release of mediators that induce inflammation [1]. Th2 cells also induce local influx of eosinophils, which release toxic products that contribute to tissue damage (Fig. 1). All these steps are regulated by cytokines. A clinical implication of this is that specific blockade against key cytokines might be used therapeutically [2]. The Th2 cell may release key cytokines, particularly interleukin (IL)-4 that promotes IgE production, and IL-5 that causes influx and activation of eosinophils. This is known as the 'Th2 hypothesis in allergy'. The hypothesis is supported by experimental and clinical studies [1]. Moreover, promising results of treating asthmatic patients with an inhaled IL-4 blocker were recently reported [3]. However, many other cytokines and cells than those implied by the Th2 hypothesis regulate allergic inflammation. Furthermore, the effects of cytokines are modulated by soluble cytokine receptors (SCRs), receptor antagonists and membrane-bound receptors.

The nose is a good model to study allergic inflammation locally and *in vivo*. Several of the components of the Th2 hypothesis have been investigated in the upper airways. The aim of this review is to summarize what is known about cytokines and their receptors in allergic rhinitis, with special reference to the Th2 hypothesis.

Do antigen-presenting cells induce proliferation of Th2 cells?

Antigen-presenting cells, particularly dendritic cells (DCs), act as mucosal sentinels, which take up, process and present

antigen to Th cells in regional lymphnodes. DCs increase in the nasal mucosa from patients with allergic rhinitis after allergen exposure [4] and may regulate the balance between Th1 and Th2 cells. Interactions between DCs and T cells from patients with allergic rhinitis result in release of Th2-cytokines [5]. By contrast, IL-12, which induces proliferation of Th1 cells, decreases [6]. The exact mechanisms by which DCs regulate Th cells have not been defined. It is likely that Th-differentiation results from interactions between DCs, Th cells and other local cells, rather than DCs directing Th cells. Such interactions involve cytokines and cell-surface molecules, which in turn are affected by the dose and type of antigen [7].

This highlights a general characteristic of how cytokines regulate cells; proliferation or activation of a cell does not necessarily occur in response to cytokines received from another cell, in a hierarchical sequence, but as a result of exchange of cytokines between the cells.

Do Th2 cells cause allergic rhinitis?

According to the Th2 hypothesis in allergy Th2 cells promote IgE synthesis, whereas Th1 cells inhibit IgE synthesis. These opposing effects are caused by differential cytokine production. Th2 cells secrete IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13, but not interferon (IFN)- γ . Th1 cells secrete IL-2, IFN- γ and tumour necrosis factor (TNF)- β , but not Th2-cytokines. Th2-cytokines regulate all components of the disease model in Fig. 1, IgE production (IL-4, IL-5, IL-6 and IL-13), growth and activation of eosinophils (IL-4, IL-5), mast cells and basophils (IL-4, IL-9 and IL-10). Th1 and Th2 cells antagonize each other, and allergic inflammation is the result of a predominance of Th2-cytokines relative to Th1-cytokines [1]. Infiltration of Th2 cells in the nasal mucosa has been described in allergic rhinitis [8,9]. The local expression of Th1- and Th2-cytokines in allergic rhinitis has also been examined, with mixed results. Low or non-detectable IFN- γ levels have been described on both the mRNA and protein level [10–15].

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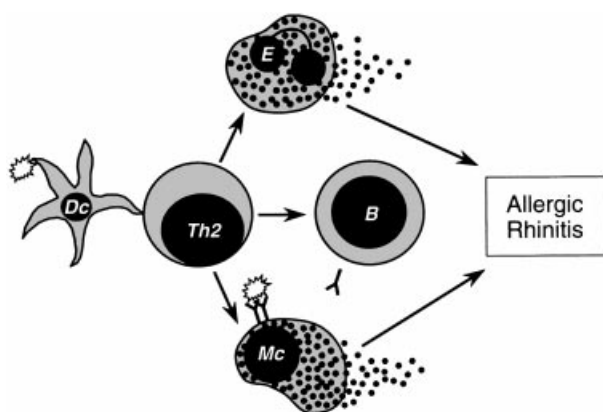


Fig. 1. Pathogenetic mechanisms in allergic rhinitis. A dendritic cell (Dc) presents an allergen to a Th cell. In allergic patients this leads to proliferation of Th2 cells, which release Th2-cytokines. These cytokines induce release of IgE from B-cells, as well as activation of mast cells (Mc) and eosinophils (E). This results in secretion of vasoactive and toxic mediators, such as histamine, eosinophil cationic protein and major basic protein, that induce allergic rhinitis.

Immunotherapy increases the number of nasal mucosal cells expressing mRNA for IFN- γ and nasal fluid levels of IFN- γ protein [12,14]. Increased IL-4 protein and mRNA [8,11,15–19] has been described. However, in three studies no, or only a few, patients had detectable levels of IL-4 protein in nasal fluids [10,14,20]. A similar pattern is seen for IL-5 in nasal fluids; increased levels of IL-5 protein have been described in three studies [15,20,21]. In two studies no increase was found [11,22] while in another IL-5 protein was reported to decrease following immunotherapy [14]. The scenario is similar in nasal mucosal tissue with either no significant increase in IL-5 [23], or an increase being shown [16,17]. An increase of IL-6 protein has been described in nasal fluids of patients with allergic rhinitis [20,24], but not by others [15]. No increase of IL-6 immunoreactivity was found in nasal biopsies [23]. In two studies of nasal fluids, IL-4/IFN- γ ratios were higher in school children with allergic rhinitis than in healthy controls [11,15].

In further support of the Th2 hypothesis, Th2 cytokines were associated with the increased presence of eosinophils, ECP and IgE, but not neutrophils, in nasal biopsies and fluids from patients with allergic rhinitis [8,11,15,18]. By contrast, IL-8, which is chemotactic for neutrophils, correlated with neutrophils [15,25].

Taken together, these observations show considerable quantitative and qualitative variation in Th2-cytokine responses. There could be methodological explanations for such variation, such as low concentrations of cytokines in biological fluids or use of different analytical methods. The variation could also have biological explanations, e.g.

variable allergen-exposure. This is supported by *in vitro* data showing that release of IL-4 from basophils is correlated to the amount of allergen used to stimulate the cells [26]. Adding further support to this concept, a comparison of cytokine responses in school children with allergic rhinitis during two seasons with high and low air pollen counts, showed that Th2 cytokines and eosinophils were higher during the season with high pollen exposure. By contrast, the Th1 cytokine IFN- γ did not differ [15]. Another explanation for variable cytokine levels could be the kinetics of Th2-cytokine responses. There are at least two stages of allergic disease, sensitization and clinical disease. It is thought that proliferation of Th2 cells has an important role during the sensitization stage [7]. The clinical disease stage is more complicated. In allergic rhinitis provocation studies have indicated the presence of early and late phase reactions, based on differential influx of cells. While Th2 cells are mainly associated with the late phase [27], no distinct phases of Th2-cytokine release have been defined in allergic rhinitis [20,24]. In asthma and atopic dermatitis Th2 profiles may predominate in acute stages, whereas more heterogeneous or even Th1-like phenotypes can be found in chronic disease [28,29]. It should also be noted that Th2-cytokines are active in tissues other than the nasal mucosa. Recent data indicate that nasal allergen exposure results in increased expression of IL-5 and its receptor in the bone marrow [30].

In summary, Th2 cells could have a causal role in allergic rhinitis. However, cytokine responses varied considerably. This could depend on variable allergen exposure or release of cytokines from Th cells at different time points and tissues. By inference, other cells and cytokines could also have causal roles in allergic rhinitis.

Other cells than Th cells release Th1- and Th2-cytokines

Th1- and Th2-cytokines can be secreted by other cells in the nasal mucosa, such as CD8⁺ T cells, NK cells, B cells, eosinophils, mast cells, basophils and epithelial cells [9,31]. Of these, mast cells and basophils may release Th2-cytokines in direct response to allergen [18,32]. This is not incompatible with the Th2 hypothesis, since Th2 cells could be the primary cause of mucosal influx of mast cells and basophils during sensitization. However, since Th2 cells, mast cells and basophils may all release Th2-cytokines during the disease stage, their relative causal roles remain to be defined. The mast cell is of particular interest in this context, since it is activated within minutes after contact with antigen, in contrast to Th2 cells and basophils, which are associated with late-phase responses. The mast cell stores IL-4 in its granules and might therefore initiate allergic inflammation, by inducing IgE synthesis, proliferation of Th2 cells and influx of eosinophils [32]. It is also

possible that a subset of T cells ($\gamma\delta$ T cells), which directly recognizes allergen, can contribute to allergic inflammation [27]. Moreover, there are other Th phenotypes than Th1 and Th2, such as Th0 that is capable of producing both Th1 and Th2 cytokines, and Th3 that mainly produces the immunosuppressive cytokine transforming growth factor β [33].

Other cytokines than Th2-cytokines could have causal roles in allergic rhinitis

Cytokines that are not usually associated with the Th2 hypothesis, may contribute to allergic inflammation. Nasal epithelial cells, neutrophils, mast cells, fibroblasts, for example, release eotaxin, IL-1 β , IL-8 and TNF α , which can induce influx and activation of eosinophils [34–36]. Cytokine release from these cells can indirectly result from interactions with Th2 cells, e.g. nasal fibroblasts exposed to IL-4 and IL-13 secrete eotaxin [36]. However, nasal epithelial cells may also release cytokines in direct response to proteolytic activity of allergens [37]. Moreover, epithelial responses occur quickly. Marked up-regulation of eotaxin mRNA was found 2 h after allergen challenge in bronchial biopsies from patients with asthma [38]. Epithelial cells could therefore have a causal role in acute allergic inflammation, in addition to Th2 cells, mast cells and basophils. Local elevations of IL-1 β , IL-8 and TNF α , have been described in some studies of allergic rhinitis [20,24,25,34,39], but not in others [15,22]. Epithelial and other cells may also release immunosuppressive cytokines [38].

It is of note that at present more than 100 cytokines are described, and an unknown number of these may partake in regulating allergic inflammation.

In summary, other cells and cytokines than those included in the Th2 hypothesis may have causal roles in allergic rhinitis (Fig. 2).

Soluble cytokine receptors, receptor antagonists and membrane-bound receptors modulate the effects of cytokines

Soluble cytokine receptors

A cytokine induces signal transduction by binding to its membrane-bound receptor. However, the cytokine can also bind to specific, soluble cytokine receptors (SCRs). SCRs generally comprise the extra-cellular portions of the membrane-bound receptors. SCRs are released either by proteolytic cleavage of membrane receptors or by direct production, as a result of alternative mRNA splicing [40]. The relative proportions of soluble and membrane-bound receptors *in vivo* are not known. In human eosinophils the

soluble IL-5 receptor (IL-5sR) comprises 95% of the total IL-5 receptor mRNA [41]. SCRs are generally also found in larger concentrations than their ligands (i.e. the specific cytokines that SCRs bind to). In allergic rhinitis the levels of SCRs may exceed those of their ligands almost 100-fold [42]. Consequently, large portions of cytokines are bound to SCRs *in vivo*. Release of SCRs may be ligand-induced. In allergic rhinitis and other diseases, SCRs were strongly correlated to their ligands and could thereby give detailed information about inflammatory processes [40,42].

Since SCRs are found in higher concentrations than cytokines, and have higher molecular weights, they are easier to measure. This has led to suggestions that SCRs could be used diagnostically [40]. SCRs can act as inhibitors, by competitively inhibiting cytokines from binding to their membrane-bound receptors (Fig. 3a). The clinical relevance of this is supported by a study of asthmatic patients showing a negative correlation between IL-5sR and bronchial obstruction, indicating that IL-5sR inhibits bronchial obstruction [41]. Moreover, the soluble TNF receptor has proved clinically useful in treating patients with rheumatoid and psoriatic arthritis [43]. IL-4sR has recently been tried against asthma in a clinical study [3]. However, SCRs may also have the opposite effect, i.e. act as enhancers (Fig. 3b). In this role SCRs protect cytokines from degradation, thereby prolonging their half-lives 10–20 fold. By having lower affinities for their ligands than the membrane-bound receptors, SCRs may deliver cytokines to the membrane-bound receptors, when the levels of free cytokines decrease [40]. The enhancing effects of IL-4sR and other SCRs are supported by experimental studies [44].

In patients with allergic rhinitis, asthma, autoimmune and infectious diseases SCRs increase and correlate with disease markers, such as eosinophils [40,42]. In allergic

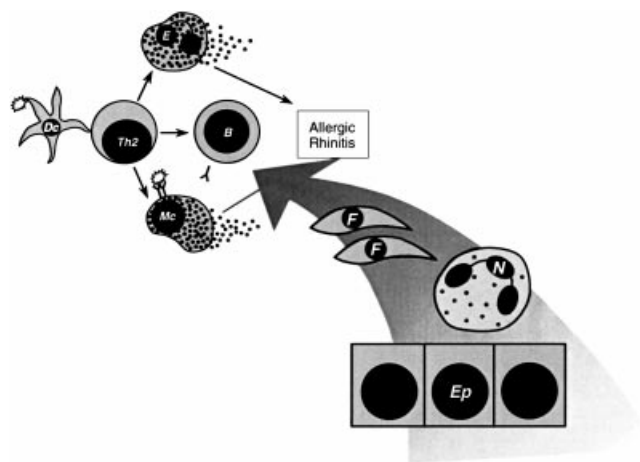


Fig. 2. Neutrophils (N), epithelial cells (Ep) and fibroblasts (F) may release cytokines that contribute to allergic rhinitis.

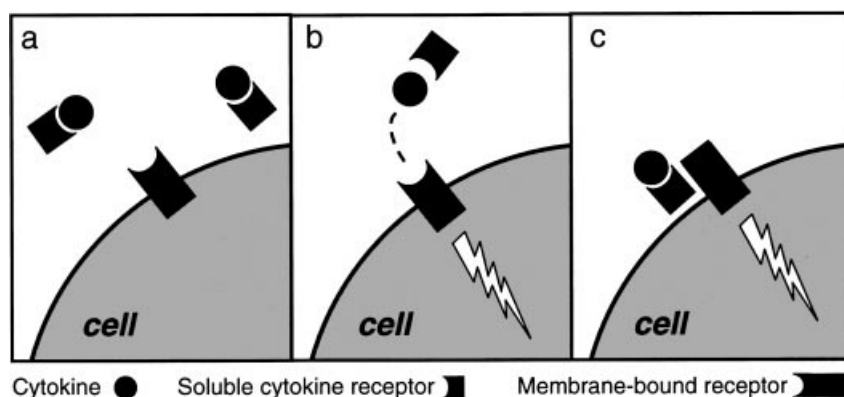


Fig. 3. Different modulatory effects of soluble cytokine receptors. (a) Inhibition. SCRs bind cytokines, thereby inhibiting the cytokine from binding to its membrane-bound receptor. (b) Enhancement. After having protected a cytokine from degradation, the SCR releases the cytokine to its membrane-bound receptor. Ligand of the cytokine to the membrane receptor induces signal transduction. (c) Enhancement. IL-6 binds to the soluble IL-6 receptor. This complex binds to another membrane-bound receptor, GP130, forming a final, signal transducing unit.

rhinitis a specific elevation of nasal fluid IL-4sR, but not of other SCRs, has been described [42]. This elevation does not contradict an inhibitory role of IL-4sR, since the increase could be an auto-inhibitory mechanism. In that case, negative correlations between IL-4sR and disease markers, such as eosinophils and IgE, would be expected, in analogy with IL-5sR in relation to bronchial obstruction. However, IL-4sR correlated positively to nasal fluid eosinophils and IgE. The other investigated SCRs, IL-1sR2, IL-6sR, TNFsR1 and TNFsR2 correlated positively with neutrophils, but not with eosinophils. Essentially, these were the same correlation patterns as those of their ligands. IL-6sR is of particular interest when interpreting the correlation patterns, because it mainly acts as an enhancer (Fig. 3c). If, in contrast, the other SCRs mainly act as inhibitors, differential correlation patterns would be expected. However, IL-6sR and the other SCRs were all positively correlated to disease markers.

Similar to cytokines, the levels of SCRs in nasal fluids vary in different studies. Both increase and no increase of TNFsR1 and TNFsR2 have been reported in allergic rhinitis [42,45]. In another study no seasonal increase of IL-4sR was found, but the levels increased after treatment with a topical glucocorticoid [11]. The latter finding was interpreted as an inhibitory effect. These apparently opposing results could be explained by experimental data showing that SCRs can act both as inhibitors and enhancers, in a dose-dependent manner; at low IL-4/IL-4sR ratios IL-4sR serves as an inhibitor, and at high ratios as an enhancer [40,44]. Thus, altered proportions between cytokines and their SCRs may be an important mechanism to alter inflammatory responses, and an alternative to release of different cytokines. There is little data about this *in vivo*. However, concern has been expressed that

treatment with SCRs could enhance, rather than inhibit, ligand bioactivity [44].

Receptor antagonists

Endogenous receptor antagonists are structural variants of cytokines, which bind cytokine receptors with high affinity but do not trigger signal transduction. The balance between cytokines and their receptor antagonists thus represents another mechanism, by which cytokine effects are modulated. Receptor antagonists for IL-1, IL-4 and IL-12 have been described [33,46]. Decreased concentrations of the IL-1 receptor antagonist have been found in allergic rhinitis [47]. Receptor antagonists may have therapeutic potential in allergic diseases and clinical studies are underway [2].

Membrane-bound cytokine receptors

Cytokines deliver signals to target cells via membrane receptors. Variable distribution and affinities of these receptors, are important determinants of how cytokines regulate inflammatory responses [33]. The effects of a given cytokine can differ depending on which cell type of the membrane receptor is found. The membrane-bound IL-4 receptor (IL-4R) has, for example, been found on epithelial cells, endothelial cells, T and B cells, mast cells, monocytes and eosinophils [48]. The effects of IL-4 on these cells do not conform to a simple, pro-allergic pattern; IL-4 induces proliferation of Th2 cells, but apoptosis in eosinophils [49]. Furthermore, the number of receptors per cell varies from 10 to $>10^4$, and has variable ligand-affinities. It is also possible that mutations in receptors, e.g. IL-4R, can lead to increased ligand-sensitivity and thereby increased risk of allergic disease

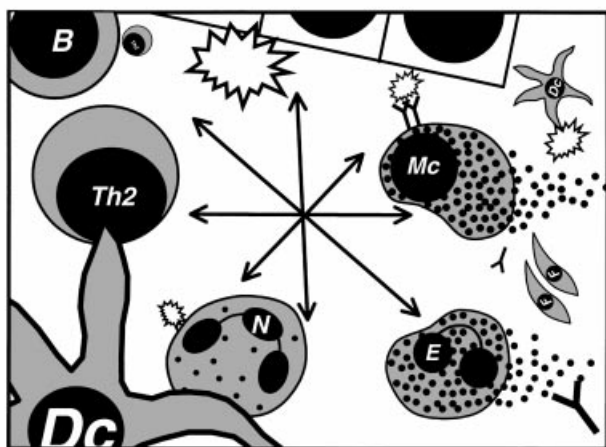


Fig. 4. The wide variety of cells expressing Th2-cytokines and receptors indicates that the cells may communicate multidirectionally, rather than sequentially. This complicates definition of the causal role of individual cell types, such as Th2 cells.

[50]. In some cases less than 100 receptors per cell are sufficient to induce an immunological response [33]. This has important implications for clinical studies of cytokines; comparisons of absolute levels of cytokines may be misleading, because of variations in numbers, affinities and sensitivities of their receptors. Moreover, the wide variety of cells expressing Th2-cytokines and receptors indicate that the cells may not communicate sequentially as in Fig. 1, but multidirectionally (Fig. 4). This further complicates definition of the causal role of Th2 cells relative to other cells. Up-regulation of IL-4R and IL-5R, and down-regulation of IL-12R has been described in nasal biopsies from patients with allergic rhinitis [6,48], but the cellular distribution of cytokine receptors in the nasal mucosa has not been defined.

Conclusions and comments

Allergic rhinitis offers an opportunity to study how cytokines regulate allergic inflammation locally and *in vivo*. The Th2 hypothesis is supported by elevations of Th2-cytokines relative to Th1-cytokines in allergic rhinitis. Similar alterations have been shown for the corresponding soluble and membrane-bound receptors. Moreover, Th2 cytokines correlated positively with eosinophils, ECP and IgE. A clinical implication of this is that therapy specifically directed against Th2 cytokines could be effective. However, the levels of Th2-cytokines varied considerably in different studies. This could depend on methodological problems. Moreover, comparisons of absolute levels of individual cytokines can be misleading, since immunological effects depend on the relative concentrations of

interacting cytokines. This is exemplified by the IL-4/IFN- γ ratio; two patients with the same IL-4 levels may have different IgE concentrations, depending on different expression of the IL-4 antagonist IFN- γ .

Furthermore, alterations in the levels of receptor antagonists, soluble and membrane-bound receptors can result in either inhibition or enhancement of IgE production. Thus, the combinations and proportions of cytokines and their receptors determine immunological effects, rather than absolute levels of individual cytokines. However, variable cytokine levels may also have biological explanations, such as variable allergen exposure. Moreover, cytokine responses may vary at different time points, e.g. Th2-cytokines could predominate in the early stages of allergic inflammation, and Th1-cytokines in the later stages. These, and other, observations have led to questions about the causal role of Th2 cells, compared to other cells [33]. First, Th2-cytokines are released by cells other than Th2 cells. Second, allergens may directly cause cytokine secretion from mast cells, basophils and epithelial cells (rather than just from Th2 cells). Moreover, the wide variety of cells expressing Th2-cytokines and receptors indicate that different cells may not release and respond to cytokines sequentially as in Fig. 1. Rather, the cells could communicate multidirectionally in networks (Fig. 4). Thus, identification of an independent cause, such as the Th2 cell, may not be possible.

An alternative perspective on causality was recently presented in this journal, based on 'connectionist theory' [51]; allergic inflammation cannot be explained by linear causality, like Th2 cells directing other cells, but by general alterations in interactions between multiple circuits within a network. These alterations could depend on defective adaptation, or training of the network, because of genetic defects in combination with environmental influences. Importantly, there is no single, independent cause, such as the Th2 cells. Instead, the Th2 cell could represent one of many circuits. The altered interactions could, for example, depend on different combinations or proportions of cytokines and receptors. As previously discussed, just changing proportions may suffice to create completely opposing effects. Changed proportions, in turn, could depend on both intrinsic and extrinsic factors, such as a gain-of-function mutation of IL-4R as well as the dose and type of antigen. A possible clinical implication is that the cell-cytokine network could be re-trained. Immunotherapy may be an example of this. It should be emphasized that the connectionist hypothesis is not substantiated by experimental data. However, research in immunology and other disciplines indicates that complex systems may have general characteristics, and that these can be described with bioinformatic methods [52]. In cytokine research multivariate methods have been applied to detect altered

combinations/proportions of cytokines [53] and computer simulations to test the effects of such alterations [52]. If applicable, such methods could perhaps contribute to understanding the complex and dynamic nature of allergic inflammation.

In summary, up-regulation of Th2-cytokines and receptors in allergic rhinitis, are compatible with the Th2 hypothesis. However, other cells and cytokines than those included in the Th2 hypothesis may have important regulatory roles.

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