Mediators in Nasal Polyposis

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Nasal polyposis (NP) is a chronic inflammatory disease of the sinuses often associated with asthma. Although we have not yet achieved a full understanding of the precise mechanisms underlying the pathogenesis of NP, recent insights have been acquired into the regulation of eosinophil chemotaxis, activation, and survival, in addition to their possible link to gross histopathologic changes such as pseudocyst formation. Interleukin (IL)-5, transforming growth factor-β_1, and eotaxin seem to be crucial players in the regulation of eosinophilic inflammation and extracellular matrix breakdown. The cytokine pattern in NP assumes neither a T helper 1 (Th1) nor Th2 type predominance, because IL-4, IL-5, IL-12, and interferon-γ have all been shown to be upregulated in NP tissue, without influence of the atopic status. However, recent studies have demonstrated a strong local upregulation of the immunoglobulin E (IgE) synthesis with the formation of specific IgE to *Staphylococcus aureus* enterotoxins, suggesting a possible role of superantigens in these pathologic processes.

Introduction

Nasal polyposis (NP) is thought to be a multifactorial disease of the nasal mucosa, which is characterized clinically by the presence of edematous masses in the nasal and paranasal cavities that result in nasal obstruction, loss of sense of smell, postnasal drip, headache, and sleep disorders. More recent evidence suggests that NP can lead to a greater impairment in the quality of life of afflicted individuals than of patients with perennial allergic rhinitis [1].

Epidemiologic studies have demonstrated that the prevalence of NP ranges from 1% to 4% in the general population, although this may be much higher in a subgroup of patients with comorbid asthma [2,3]. NP also frequently develops in patients with other respiratory conditions, such as chronic rhinitis or sinusitis, aspirin intolerance, cystic fibrosis, and primary ciliary dyskinesia, in which airway mucosal disease is widespread. However, it has been suggested that the predominant type of polyps, which cover 80% to 90% of polyp disease in Europe and the United States, are bilateral, eosinophilic, and frequently linked to asthma and aspirin intolerance [4]. Although nasal polyps respond well to treatment with systemic and topical corticosteroids, currently there are no medical or surgical interventions that guarantee a complete cure. Furthermore, management of patients with severe NP is often unsatisfactory, and made more difficult as a consequence of a high recurrence rate.

The precise mechanisms underlying the pathogenesis of NP are not clearly understood and are compounded by the fact that there is lack of a widely accepted classification, which includes both clinical history and histology to differentiate between the various forms of NP. Recurrent infections, rupture of the epithelium and production of granulation tissue, inhaled or food allergens, T-cell disturbances, and aerodynamic factors have all been suggested to play a role in the pathogenesis of nasal polyps [5]. Studies have failed to show an increased prevalence of NP in patients with atopy or allergic disorders, compared with the general population [6]. Some studies have demonstrated that the development of nasal polyps seems higher in patients with nonallergic rhinitis and nonallergic asthma, compared with their allergic counterparts [7], and symptoms and eosinophilic inflammation in seasonal allergic patients are not necessarily influenced by the season [8]. Other studies have demonstrated that tissue immunoglobulin E (IgE) concentrations are increased in NP, irrespective of skin test positivity, suggesting the possibility of local IgE production [9].

Histologic examination of polyp tissue has demonstrated that a damaged epithelium, a thickened basement membrane, chronic inflammation, and reduced numbers of vessels and glands with virtually no nerves in the stoma are prominent features of polyps [4]. The inflammation in polyps is primarily comprised of mast cells, lymphocytes, neutrophils, and eosinophils, of which eosinophils are the most abundant cell type and present in the vast majority of bilateral nasal polyps.

Mediators Influencing Eosinophilic Inflammation

Because of the prominence of eosinophilic inflammation associated with the majority of nasal polyps (Fig. 1) and the potential of eosinophils to elicit tissue damage and subsequent remodeling, it is likely that a better understanding of

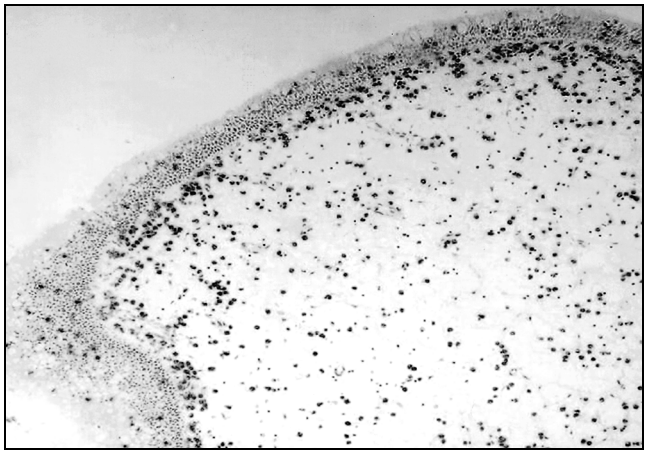

Figure 1. EG2-stained nasal polyp showing a subepithelial eosinophilic inflammation. (Original magnification, 100×).

the mechanisms underlying the migration, activation, and maintenance of eosinophils in nasal polyp tissue will be a key to understanding the etiology and pathogenesis of nasal polyps. Several studies have demonstrated that a variety of cytokines, chemokines, and adhesion molecules play important roles in eosinophil function.

Cytokines

A review of the cytokines that can modulate the function of eosinophils has shown that these include interleukins (IL)-1α, IL-3, IL-4, IL-5, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), transforming growth factor (TGF)-β, and tumor necrosis factor (TNF)-α [10]. IL-3, IL-5, and GM-CSF regulate the differentiation, growth, and survival of eosinophils, and are effective eosinophil primers for activation by other agonists. Although some studies of TNF-α have demonstrated that it can also enhance eosinophil survival in vitro, this cytokine and IL-1 have been more extensively investigated for their ability to modulate the expression of several endothelial and epithelial cell adhesion molecules, necessary for intertissue trafficking of the eosinophils [11]. Similarly, IL-4 has also been shown to increase the expression of vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells [12]. In contrast, studies of IL-10 and TGF-β have demonstrated that these cytokines may downregulate eosinophilic inflammation, because they can either inhibit the synthesis or abrogate the eosinophil survival-prolonging effects of IL-3, IL-5, and GM-CSF, thus inducing their apoptosis [13].

The biologic role of TGF-β, however, is more complex and its effects on structural cells, such as fibroblasts, are thought to be important especially in the regulation of fibrosis and tissue remodeling [14]. TGF-β is also a key regulator in the maintenance of the immunologic homeostasis because of its significant anti-inflammatory and immunosuppressive properties. Similarly, although in vitro studies have suggested that IL-4 may also possess potentially anti-inflammatory properties, this cytokine is thought to be important in allergic disease, due to its key role in the expression and synthesis of IgE and IgE receptors [15].

In spite of the influence of a large array of cytokines affecting the activity of eosinophils, these studies collectively suggest that IL-5 is likely to be one of the most important mediators that influence eosinophils, because of its specificity as an eosinophilopoietic factor [16], and its synergism with eotaxin in mobilizing bone marrow eosinophils into the circulation, resulting in their recruitment and accumulation in vivo [17]. IL-5 also acts synergistically with TNF-α to enhance eosinophil activation (degranulation) and induces expression of intercellular adhesion molecule-1 (ICAM-1) on the eosinophil surface membrane [18].

Chemokines

The chemokines affecting leukocytes have recently been reviewed extensively [19]; it has been demonstrated that RANTES (regulated upon activation in normal T cells expressed and secreted), eotaxin, macrophage inflammatory protein, monocytes chemotactic protein (MCP), and myeloid progenitor inhibitory factor increase eosinophil chemotaxis. Of these chemokines, RANTES and eotaxin are of particular significance. Studies of RANTES have demonstrated that in addition to chemotaxis, this mediator also induces transendothelial migration of eosinophils and leads to activation of eosinophils, resulting in the release of cytotoxic agents such as superoxide and eosinophilic cationic protein (ECP) [20,21]. Similarly, eotaxin has also been shown to activate eosinophils, but unlike RANTES and other chemokines affecting eosinophil activity, eotaxin is particularly selective for eosinophils [22].

Cell adhesion molecules

A review of the mechanisms underlying active mobilization of eosinophils into the airways has demonstrated that this involves a variety of adhesion molecules expressed on both the eosinophils and endothelial cells, and include members of the immunoglobulin superfamily (*eg*, VCAM-1, ICAM-1), β_1 and β_2 integrins (*eg*, very late antigen appearing antigen [VLA]-4 or $\alpha_4\beta_1$; CD11a/CD18 or $\alpha_L\beta_2$), and selectins (*eg*, E-selectin, P-selectin) [23]. It has been suggested that interactions between VLA-4 and VCAM-1, and between CD11a/CD18 and ICAM-1, respectively, expressed on eosinophils and cytokine-activated endothelial cells in the bone marrow and the airways, are of particular importance for transendothelial migration of eosinophils. The interaction between VLA-4 and VCAM-1 may also modify the activation and effector functions of eosinophils by modifying the activation state of the β_2 integrins expressed on eosinophils [24].

Studies in Nasal Polyps

Cytokines

A large body of studies have demonstrated that several eosinophilic mediators are present in nasal polyp tissue, and that different cell types generate these mediators. Early studies by Denburg *et al.* [25] demonstrated that conditioned medium

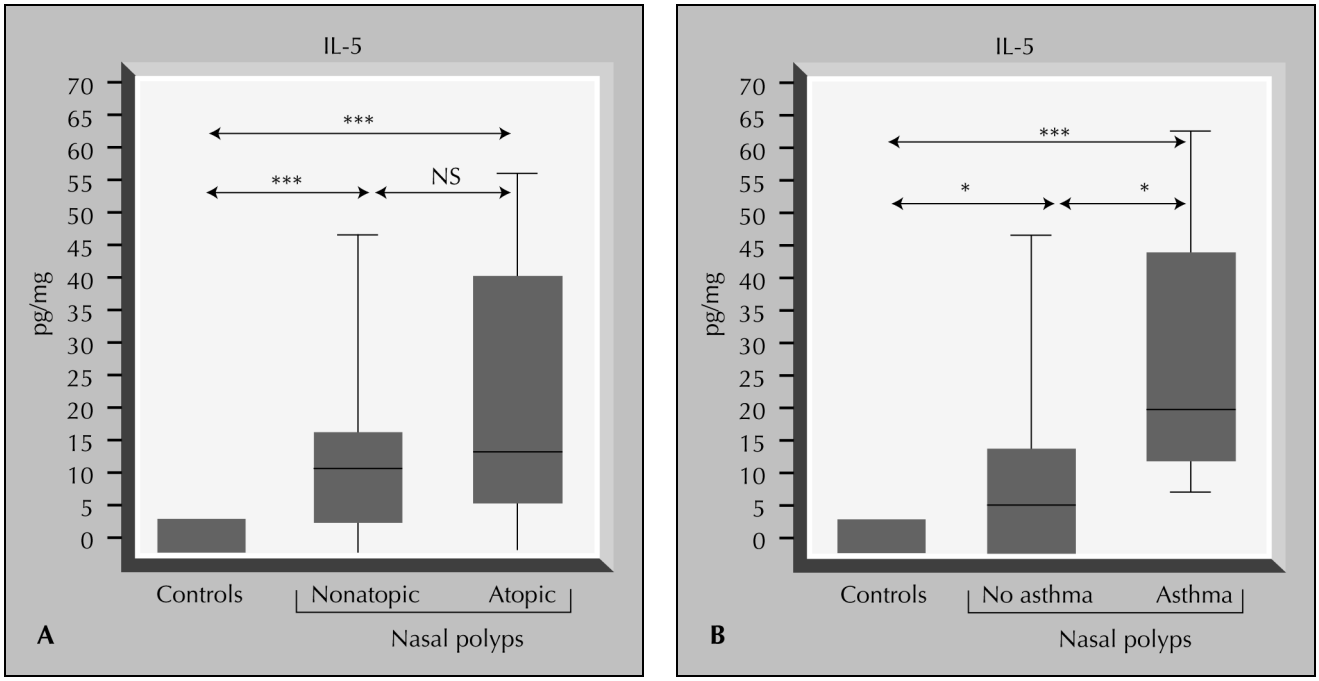

Figure 2. A and B, Comparison of interleukin (IL)-5 concentrations in inferior turbinates (controls) and nasal polyp tissue of atopic, nonatopic, asthmatic, and nonasthmatic patients. This Box-and-whisker plot represents the median and the 10th, 25th, 75th, and 90th percentiles. Statistical analyses performed by the Mann Whitney two-tailed test for unpaired comparisons. *$P < 0.05$; ***$P < 0.001$. NS—not significant.

derived from cultured human nasal polyp epithelial scrapings contained potent eosinophil colony-stimulating activities and an IL-3-like activity, suggesting that the accumulation of eosinophils in polyps may be a result of in situ growth and differentiation of progenitors stimulated by soluble hematopoietic factors derived from mucosal cell populations. Subsequent studies by this group and others have shown that nasal polyp epithelial cell-conditioned medium contains greater quantities of GM-CSF, G-CSF, and IL-6 than conditioned medium obtained from normal nasal epithelial cell cultures [26]. Investigation of nasal polyp tissue has also indicated that there is increased expression of GM-CSF, at both the mRNA and protein levels, and that a number of cell types, including epithelial cells, fibroblasts, monocytes, and eosinophils, are involved in the synthesis of this cytokine [27–29].

Hamilos *et al.* [30] have investigated polyp tissue samples from patients with allergic or nonallergic chronic hyperplastic sinusitis with nasal polyposis (CHS/NP) and nasal turbinate biopsy specimens from normal control patients by in situ hybridization. They found that patients with allergic CHS/NP had significantly higher tissue densities of GM-CSF, IL-3, IL-4, and IL-5 transcripts compared with normal controls. In contrast, patients with nonallergic CHS/NP had significantly higher tissue densities of GM-CSF, IL-3, and interferon (IFN)-γ transcripts. From these results, the authors concluded that distinct mechanisms of eosinophilia existed in patients with allergic versus nonallergic CHS/NP, and that in the nonallergic patients, eosinophilia was unlikely to be influenced by IL-4 and IL-5.

For our own studies, we selected patients with bilateral NP, based on nasal endoscopic examination, and excluded chronic sinusitis patients, based on histologic and mediator protein pattern, as described in a recent review [31]. Furthermore, we investigated primarily cytokine protein concentrations in polyp tissue homogenates in order to circumvent any difficulties in interpretation of the findings, which could result from compartmental differences in cell numbers. In the first study, we investigated protein concentrations of different cytokines and chemokines in polyps from 23 patients and turbinate tissue from 18 healthy individuals [32]. This study demonstrated that IL-6, IL-8, IL-10, Gro-α, RANTES, and TNF-α proteins were present in greater quantities in polyp tissue compared with control turbinate tissue, although the differences were not statistically significant. In contrast to findings reported before, IL-3 was not detectable, and GM-CSF was found in only a small number of polyps and control turbinate samples. The most striking features of our study, however, were that: 1) IL-5 was found in 18 of 23 nasal polyps, compared with only one of 18 turbinate tissues from healthy controls (Fig. 2); 2) the concentration of this cytokine was independent of the atopic status of the patient; and 3) the highest concentration of IL-5 was found in subjects with asthma and aspirin sensitivity.

Immunohistochemical analysis of polyp tissue also demonstrated that about 70% of the large numbers of IL-5-positive cells were eosinophils, suggesting a possible autocrine role for IL-5 in the activation of eosinophils. We have also demonstrated that there is a strong correlation

between concentrations of IL-5 protein and ECP [33••], a marker of eosinophil activation, and that treatment of eosinophil-infiltrated polyp tissue with neutralizing anti-IL-5 monoclonal antibody, but not anti-IL-3 or anti-GM-CSF monoclonal antibodies in vitro, resulted in eosinophil apoptosis and decreased tissue eosinophilia [34••]. In contrast, unilateral antrochoanal polyps demonstrated a marked paucity of eosinophils and IL-5 [35]. Collectively, our studies suggest that increased production of IL-5 is likely to influence the predominance and activation of eosinophils in nasal polyps.

The finding of a lack of difference in the amounts of cytokines detected in polyps from allergic or nonallergic patients is in accordance with recent studies, which have investigated either the expression of cytokine mRNA in nasal polyp tissue, or studied the production of cytokines by local cells using the Elispot technique. Ming *et al.* [36] evaluated the expression of mRNAs for IL-4, IL-5, and IFN-γ in nasal polyps and turbinate specimens from patients with and without allergic rhinitis, and found no significant difference in the expression of any cytokine mRNA due to allergy. More recently, this group has extended their studies to compare gene expression for IL-1β, IL-6, IL-8, and TGF-β in nasal polyp tissues of patients undergoing polypectomy for nasal obstruction, and in normal turbinate tissues [37]. Southern blot analysis showed that there were no differences in the mean density ratios of any of the cytokine bands noted in polyp tissues obtained from allergic or nonallergic patients, thus confirming their previous findings. Wagenmann *et al.* [38] evaluated the number of cells expressing IL-4, IL-5, IL-12, or IFN-γ in allergic and nonallergic polyps by the Elispot technique, and demonstrated that there were no differences between the allergic versus nonallergic polyps in this regard. Furthermore, these authors demonstrated that both T helper 1 (Th1) and Th2 type cytokines were upregulated in eosinophilic NP, irrespective of allergen skin test results.

The relation of tissue eosinophilia to polyp formation remains largely unclear, whereas the expression of TGF-β_1 and TGF-β_2, predominantly by eosinophils, and their putative effects on fibroblast activity and pathogenesis of nasal polyps have been suggested in several studies [14,31,39,40]. In an approach to study possible relationships between eosinophilic inflammation and changes in extracellular tissue components, we measured IL-5, eotaxin, ECP, TGF-β_1, and albumin in nasal tissue homogenates of NP patients, who were either untreated or treated with oral glucocorticosteroids (GCS), and control subjects [41]. IL-5 was measurable in most of the untreated NP, but was not detected in any of the controls nor in the polyps of four of five patients treated with oral GCS. The comparison between the untreated polyp group and control group also showed significantly higher concentrations of IL-5, eotaxin, ECP, and albumin, and significantly lower concentrations of TGF-β_1 in polyp supernatants. In the oral GCS-treated group, IL-5, ECP, and albumin were significantly reduced, compared with untreated nasal polyps, whereas TGF-β_1 was increased. These observations suggest a deposition of albumin and other plasma proteins as a possible pathogenic principle of polyp formation and growth, which may be regulated by the subepithelial eosinophilic inflammation.

Histomorphologic analysis of early- and late-stage nasal polyps shows the presence of eosinophils, forming a subepithelial cap over a pseudocyst area filled with albumin, but not demonstrating signs of fibrosis [41]. The breakdown of extracellular matrix proteins, which may be mediated by metalloproteases, leads to the formation of "empty" pseudocysts, and is a very interesting common feature of NP histology awaiting further research. However, IL-5 and TGF-β_1 seem to represent cytokines with counteracting activities, with a low TGF-β protein concentration in IL-5-driven NP. TGF-β_1 is a potent fibrogenic cytokine that stimulates extracellular matrix formation, acts as a chemoattractant for fibroblasts, but largely inhibits the growth and activity of invading inflammatory cells.

Alam *et al.* [13] demonstrated that TGF-β inhibits the synthesis of IL-5, abrogates the survival-prolonging effect of hematopoietins (*eg*, IL-5 and GM-CSF) on eosinophils, and induces apoptosis. They suggested that there is a fine balance between the productions of TGF-β and IL-5 by eosinophils and that TGF-β may act as a homeostatic regulatory mechanism that counteracts the action of IL-5 and programs cell death. Other data showed that TGF-β in low concentrations could induce eosinophil chemotaxis, whereas higher concentrations reduce eosinophil survival mediated by IL-5, IL-3, and GM-CSF [42]. However, the major form of regulation of TGF-β activity is by post-translational modifications, which occur intracellularly and after the release of TGF-β into the extracellular environment.

Transforming growth factor-β is released in a biologically inactive form termed the "small latent complex," in which the mature TGF-β molecule is noncovalently bound to the latency-associated peptide. Another protein, termed latent TGF-β binding protein (LTBP) may be covalently coupled to the small latent complex, the resulting structure being called the "large latent complex," preventing TGF-β binding to receptors. This process of extracellular post-translational modification can influence the amount of active TGF-β available at specific sites and under specific conditions [43]. The presence of LTBP, for example, serves to direct TGF-β to the extracellular matrix. Staining of nasal polyp tissue shows that TGF-β_1 is mainly bound to the extracellular matrix, serving as a reservoir for latent TGF-β_1, where it awaits activation. Our data show that concentrations of latent TGF-β are up to 100-fold higher than active TGF-β. Thus, conditions are optimal for a severe eosinophilic inflammation in NP, where high levels of IL-5 and low concentrations of both latent and active forms of TGF-β are present (Fig. 3).

As discussed earlier, early studies have demonstrated that tissue IgE concentrations and the number of IgE-positive cells may be increased in NP, suggesting the possibility

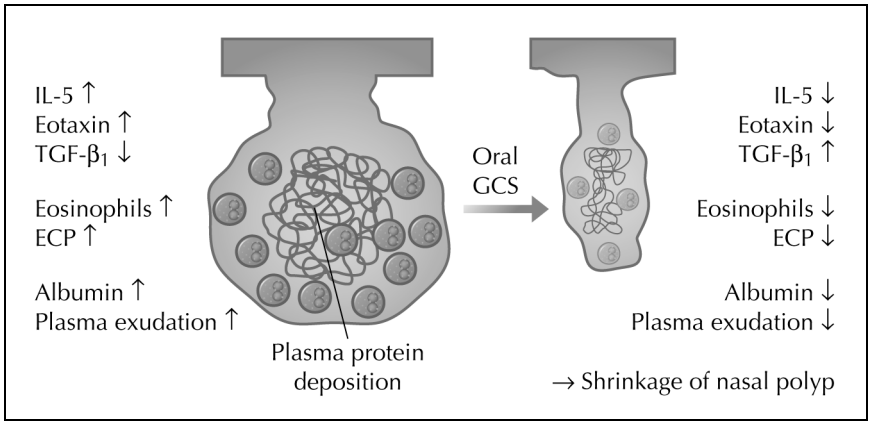

Figure 3. A model of the current understanding of the pathophysiology of nasal polyposis and the impact of oral glucocorticosteroid (GCS) treatment. ECP—eosinophilic cationic protein; IL-5—interleukin-5; TGF—transforming growth factor.

of local IgE production [9]. In order to determine whether there is an association between total and specific IgE to a variety of allergens and mediators of eosinophilic inflammation in polyp tissue, we recently performed a study in which homogenates of nasal tissues from 20 NP and 20 non-polyp subjects were analyzed [33••]. With reference to findings in atopic dermatitis, IgE to *Staphylococcus aureus* enterotoxins (SAEs) were also analyzed. This study demonstrated that concentrations of IL-5, eotaxin, LTC4/D4/E4, sCD23, ECP, and total IgE were significantly higher in NP tissue, compared with non-polyp tissue, and findings for all mediator concentrations were independent of skin prick test results. Furthermore, IL-5, eotaxin, LTC4/D4/E4, sCD23, ECP, and a number of eosinophils in NP tissue were significantly correlated with tissue total IgE. A detailed analysis of IgE indicated for the first time that specific IgEs to SAEs were present in NP tissues and that these were associated with severe local eosinophilic inflammation and systemic airway disease. In those polyps with specific IgEs to SAEs, a multiclonal-specific IgE formation to inhalant allergens, high levels of tissue total IgE, and a high prevalence of asthma and aspirin sensitivity were demonstrated. These studies suggest that SAEs possibly act as superantigens through unconventional interaction with the T-cell receptor, as has been shown for atopic dermatitis [44••], and may be important in the pathogenesis of NP due to their potential role as disease modifiers.

Chemokines

Several recent studies have shown that nasal polyps also express high levels of RANTES and eotaxin, the predominantly recognized eosinophil chemoattractants. Using gene-specific primers in semiquantitative reverse transcriptase-polymerase chain reaction, Bartels *et al.* [45] showed that expression of eotaxin and RANTES mRNA, but not MCP-3 mRNA, was elevated in nonatopic and atopic nasal polyps, when compared with normal nasal mucosa. Similarly, Jahnsen *et al.* [46] demonstrated that mRNA expression for eotaxin, eotaxin-2, and MCP-4 was significantly increased in nasal polyps, compared with turbinate mucosa from the same patients. Moreover, expression of eotaxin-2, the novel CCR3-specific chemokine, was found to be the most prominent of the three chemokines investigated. According to the data on cytokine proteins measured in our studies [32,33••,41], it appears that eotaxin, rather than RANTES, in cooperation with IL-5, plays a key role in chemoattraction and activation of eosinophils in NP tissue. This is in accordance with the findings of a recent extensive study of about 950 nonallergic or allergic polyps, which also suggested that nasal polyp eosinophilic infiltration and activation may correlate mainly with increased eotaxin gene expression, rather than with RANTES expression. Tissue eosinophilia and nasal ECP levels were significantly correlated with eotaxin mRNA, but not RANTES mRNA expression [47].

Cell adhesion molecules

Compared with studies of cytokines and chemokines that influence the activity of eosinophils in nasal polyps, similar studies of cell adhesion molecules are relatively few. Early studies by Symon *et al.* [48] demonstrated that ICAM-1, E-selectin, and P-selectin were well expressed by nasal polyp endothelium, whereas VCAM-1 expression was weak or absent. Furthermore, monoclonal antibody against P-selectin, but not monoclonal antibodies against E-selectin, L-selectin, ICAM-1, VCAM-1, VLA-4, and lymphocyte function-associated antigen (LFA)-1, almost completely inhibited eosinophil adhesion to nasal polyp endothelium, suggesting that P-selectin was the most important adhesion molecule expressed in nasal polyps for adhesion and infiltration of eosinophils. Although P-selectin is likely to play a role in the adhesion of eosinophils to nasal polyp endothelium, the finding that monoclonal antibodies to neither ICAM-1, VCAM-1, VLA-4, nor LFA-1 had any effect on eosinophil adhesion to the endothelium is rather surprising and contrary to the findings of a large number of studies [23].

An elegant study by Jahnsen *et al.* [], using three-color immunofluorescence staining, has demonstrated that both the number of eosinophils and the proportion of vessels positive for VCAM-1 were significantly increased in the nasal polyps of 15 patients, compared with the turbinate mucosa of the same patients. More recent studies have confirmed the findings of this study and additionally demonstrated that treatment with topical GCS decreases

the density of eosinophils and expression of VCAM-1 in polyps [50]. Similarly, studies of ICAM-1 have demonstrated that this adhesion molecule is also expressed on polyp endothelial cells and that treatment with topical GCS decreases its level of expression.

Conclusions

Although we have not yet achieved a full understanding of the precise mechanisms underlying the pathogenesis of NP, recent insights have been acquired into the regulation of eosinophil chemotaxis, activation, and survival, as well as their possible link to gross histopathologic changes such as pseudocyst formation. Tissue eosinophilia, plasma exudation, and extracellular matrix breakdown with consecutive albumin retention are the most prominent pathologic features of the majority of nasal polyps. Although a large variety of mediators that influence the function and activity of eosinophils have been detected in increased concentrations in nasal polyps, compared with normal nasal turbinate tissue, current evidence suggests that IL-5 and eotaxin interact to orchestrate an intense eosinophilic inflammation. IL-5-driven inflammation is likely to be further enhanced by downregulation of TGF-β_1, a cytokine that can potentially counteract the effects of IL-5 and the breakdown of extracellular matrix. However, the cytokine pattern in NP assumes neither a Th1 nor Th2 type predominance, because IL-4, IL-5, IL-12, and IFN-γ have all been shown to be upregulated in the nasal polyp tissue. It is also not dictated by the atopic status of an individual.

Our studies have demonstrated a strong, and most probably local, upregulation of IgE synthesis, with the formation of specific IgE to SAEs and a multiclonal IgE response to inhalant allergens. Furthermore, specific IgEs to SAEs in polyp tissue were related to a severe local eosinophilic inflammation and to systemic airway diseases such as asthma and aspirin sensitivity. Consequently, it is possible that SAEs may act as superantigens and thus may induce a multiclonal T- and B-lymphocyte stimulation, with an additional activation of eosinophils, epithelial cells, antigen-presenting cells, and macrophages.

Glucocorticosteroid treatment currently represents a standard approach to NP disease, and has been shown to downregulate several markers of eosinophilic inflammation as well as vascular leakage and albumin retention. However, the understanding of NP pathophysiology achieved from recent studies suggests that there may be new targets for future therapy, including IL-5 in particular, eotaxin, IgE, and *Staphylococcus aureus* colonization, each of which may provide an effective means for the management of NP.

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