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# Nasal polyposis: eosinophils and interleukin-5

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**Key words:** anti-IL-5 antibody; apoptosis; interleukin-5 (IL-5); nasal polyposis; nasal polyps.

**Abbreviations:** ASA: acetylsalicylic acid; CF: cystic fibrosis; ECP: eosinophil cationic protein; GM-CSF: granulocyte/macrophage colony-stimulating factor; ICAM-1: intercellular adhesion molecule-1; IFN- $\gamma$ : interferon-gamma; LTC: leukotriene; MBP: major basic protein; NARES: nonallergic rhinitis with eosinophilia syndrome; NOS: nitric oxide synthase; PAF: platelet-activating factor; PDGF: platelet-derived growth factor; RANTES: regulated on activation, normal T-cell expressed and secreted; Th: T helper cell; TNF: tumor necrosis factor; VCAM-1: vascular cell adhesion molecule-1; VPF/VEGF: vascular permeability factor.

## Nasal polyposis

Nasal polyps, or diffuse nasal polyposis, were first recognized as an illness over 3000 years ago. An excellent historical survey of the treatment of nasal polyps has been given by Vancil (1). The former methods of extirpation of polyps are quite similar to currently used forms of surgery; e.g., Hippocrates developed two surgical methods of nasal polypectomy around 400 BC, the first being extraction of the polyps by pulling a sponge through the nasal canal and the second being cauterization.

Nasal polyps occur in all races and social classes (2). Hosemann et al. (3) suggested a prevalence of the disease of 1–2% of the adult population in Europe (prevalences of 0.2–28% were reported in their review). The predominance of males over females with a ratio of 2–4:1 is remarkable (2), although not confirmed by all authors (4). A hereditary factor in the development of nasal polyps has been

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considered (5). Furthermore, it is important to note that the age of manifestation of this disease is usually after the age of 20. The manifestation of nasal polyposis in children is very rare – an incidence of 0.1% has been reported (4). However, nasal polyps associated with cystic fibrosis (CF) is an exception, and is frequently found in children.

Animals, in general, do not suffer from nasal polyps, a fact which makes it difficult to study the disease in an animal model. The chimpanzee is the only animal known to suffer from a similar polyposis (2).

Nasal polyps can frequently point to a manifestation of other systemic diseases. Over the years, many attempts have been made to link nasal polyps to allergies. Numerous publications have demonstrated that in patients suffering from nasal polyps there is no higher incidence of allergies and no elevated rates of positive allergy skin tests (6, 7). However, for a small subgroup of patients with nasal polyposis, an IgE-mediated mechanism and elevated incidences of allergies have been reported even in recent publications (8). We found equally increased levels of IgE within nasal secretions of nonallergic patients with nasal polyps and within the nasal secretions of patients suffering from allergic rhinitis (9), leaving the role of IgE in nasal polyposis unclarified.

However, several illnesses and symptoms are related to nasal polyps. Some 20–50% of patients with nasal polyposis suffer from bronchial asthma, whereas nasal polyposis has been found in 20–40% of adult patients suffering from bronchial asthma (10, 11). Nasal polyps are also statistically more common in patients with nonallergic, steroid-dependent asthma than in those with allergic asthma (4). These polyps usually occur about 10 years after the onset of asthma. Furthermore, polypectomy does not aggravate or cause asthma (12).

Intolerance of acetylsalicylic acid (ASA), or of other nonsteroidal antiphlogistics such as indomethacin or ibuprofen, is associated with nasal polyps as well. Some 8–36% of patients with nasal polyps suffer from ASA intolerance (2, 4, 13, 14), and in up to 60% of patients suffering from ASA intolerance, nasal polyps have been found (10). The triad of nasal polyps, ASA intolerance, and asthma was first described by Widal et al. in 1922 (15). This association was later emphasized by Samter & Beer in 1967 (16). Their triad has been found in 36–39% of examined patients with nasal polyps (10, 11).

Patients with primary ciliary dyskinesia syndrome are known to suffer from recurrent rhinosinusitis and otitis media due to malfunction of the cilia. This is caused by a lack of dynein in microtubules. Furthermore, hypoplastic or

aplastic frontal sinuses are regularly found in these patients, and this illness is associated with nasal polyposis as well. The maximal manifestation of the illness, known as Kartagener's syndrome, is characterized by chronic sinusitis, situs inversus, bronchiectasis, and nasal polyps. Kartagener's syndrome is a rare genetic condition with an estimated incidence of 1:20 000 births (17, 18).

Another comorbid disease with nasal polyposis is CF. CF, one of the most frequent hereditary diseases found in Caucasians, is caused by an autosomal-recessive defect of the CFTR gene on chromosome 7 (coding for a chloride channel). This defect causes digestive and respiratory malfunction through a disturbance of exocrine gland function. Some 6–48% of CF patients suffer from nasal polyps (4, 10, 11, 19). As previously mentioned, nasal polyps in combination with CF are frequently diagnosed in childhood, making it necessary to exclude CF when treating children with nasal polyps.

Furthermore, the frequency of nasal polyps is also strongly associated with allergic fungal sinusitis; about 85% of cases of the latter disease are associated with nasal polyps (20).

Other coincidences of nasal polyposis include the Churg-Strauss syndrome (50% of these patients suffer from nasal polyps [4]), intolerance of alcohol (50% of patients suffering from nasal polyps are intolerant of alcohol [10]), Young's syndrome (characterized by chronic sinusitis, azoospermia, and nasal polyposis [11]), and NARES (19% of patients suffering from NARES have nasal polyps [21, 22]).

## Clinical symptoms

Nasal polyps are usually bilateral, multiple, and freely movable. Visually, they are glistening, pale-gray, smooth, and semitranslucent in appearance. Nasal polyps are attached by a pedicle and arise from the osteomeatal complex, most often from the uncinate process of the ethmoid bone and the middle turbinate (19). Nasal polyps are found most frequently on the concave site of the deviated septum, the site of higher airflow (10).

Clinical symptoms of nasal polyposis are largely caused by the diminished airflow through the nose and include dull headaches, obstruction of the airflow through the nose, rhinophonia clausa, hypo- or anosmia, snoring, postnasal dripping, and/or nasal secretion. In a few rare cases, nasal polyps may cause Woake's syndrome, resulting in bone destruction and hypertelorism (17).

Inverting papilloma or choanal polyp, as well as malignant tumors, must be considered in the differential diagnosis in

unilateral manifestation of the disease. Meningocele, encephalocele, or glioma must also be considered in children.

The clinical grading system of nasal polyps presented by Rasp & Bujia proved to be useful for clinical evaluation and follow-up. It distinguishes four grades:

- I: polyposal swelling of the mucosa of the middle meatus
- II: nasal polyps within the middle or lower meatus
- III: polyps extending over the middle turbinate
- IV: nasal polyposis with protrusion into the anterior nose (23).

The common type of treatment of nasal polyps is endoscopic functional sinus surgery, followed by treatment with glucocorticoids. A follow-up treatment with glucocorticoids is known to reduce recurrence of the disease. Although few publications have dealt with recurrence rates, recurrence constitutes a serious clinical problem. The rate of recurrence is higher in patients suffering from bronchial asthma and/or ASA intolerance (2), as well as in patients with positive allergy skin tests (24). Rates of recurrence of approximately 50% 6 months after endoscopic surgery (25) and a general rate of recurrence of up to 40% have been reported (4, 26).

Several authors could demonstrate positive effects of locally or systemically applied glucocorticoids of 50–90% (2, 23, 27, 32). Therefore, some authors suggest a conservative approach with glucocorticoids before surgery. It is important to note that nasal polyps associated with CF, primary ciliary dyskinesia syndrome, or Young's syndrome do not respond to glucocorticoids.

Experimental therapeutic approaches with roxithromycin (33), locally applied furosemide (34, 35), or H<sub>1</sub>-antagonists (36, 37) have shown no clinical relevance so far.

## Histologic findings

Nasal polyps are characterized by a pseudostratified ciliated columnar epithelium, thickening of the epithelial basement membrane, and few nerve endings (24). In general, the stroma of nasal polyps is edematous. The vascularization is poor and lacking in vasoconstrictory innervation, with the exception of the nerve terminals at the base of the polyp.

Tissue eosinophilia is a general characteristic of nasal polyps and is found in 80–90% of all cases (2). The edematous-eosinophilic type is the predominant histologic type, with an incidence rate of 86% (38). Hyperplasia of the seromucous glands has often been found. The neutrophil, fibroinflammatory type predominates in approximately 7%

of all cases. This histologic type is often found in cases associated with CF, primary ciliary dyskinesia syndrome, or Young's syndrome (4). Its polyps, as previously noted, do not respond well to corticoids (10, 11, 19) because they lack corticosteroid-sensitive eosinophils in the stroma and the polyp itself.

Both types of mast cells, with most being degranulated, are found in increased numbers within the stroma of nasal polyps (10, 39). A non-IgE-dependent mechanism of the histamine release from mast cells has been reported (40). Increased numbers of plasma cells, lymphocytes, and myofibroblasts have been found at the cellular level (41).

To summarize, the stroma of nasal polyps is cell-poor, and no marked characteristics other than tissue eosinophilia can be found. "The histologic characteristic of nasal polyps is really how unremarkable they are" (10).

## Pathogenesis

The pathogenesis of nasal polyps is far from clear. Initially, nasal polyps were thought to be of neoplastic origin (2). Furthermore, an infection was deemed unlikely to be the cause of the disease (2, 11). Numerous recent theories explain the current histologic findings by initial inflammation at the beginning of the pathologic process. These theories, however, do not sufficiently explain the cause of the postulated inflammatory process and do not distinguish between the cause and effect of the observed histologic alterations. None of the currently discussed theories seem adequate to account for all the known facts related to nasal polyps. A summary has been provided by Tos et al. (42). Bernstein et al. found alterations of the bioelectricity of sodium and chloride channels in the nasal mucosa (43, 44). The alterations could result from an initial inflammation causing edema.

The vasomotor-imbalance thesis is based on the cell-poor stroma of nasal polyps, which is poorly vascularized and lacks a vasoconstrictory innervation. It postulates that increased vascular permeability and impaired vascular regulation cause reduced detoxification of mast-cell products such as histamine. The prolonged effects of substances such as histamine within the polyp stroma then result in a marked edema, augmented by the obstruction of venous drainage. This reduction in venous drainage is of particular importance at the pedicle of the polyp (2, 10, 11, 42). The so-called epithelial rupture theory is based on a rupture of the epithelium due to edema or increased tissue turgor in illnesses such as allergies or infections. This rupture is

thought to cause polyp formation, leading to a prolapse of the lamina propria mucosae, followed by epithelialization and the gradual formation of small polyps. Gravitational effects and/or the already described obstruction of venous drainage augment the formation of nasal polyps (42).

The overall problem with all theories based on diffuse edema is that they cannot explain why polyp formation occurs in one particular area of the nasal mucosa only.

## Chemical mediators

The stroma of nasal polyps and numerous mediators, cytokines, growth factors, and adhesion molecules are currently a matter of intense research. A brief overview is given below.

Vasoactive amines, serotonin, prostaglandins, leukotrienes (LTC), norepinephrine, kinins, esterases, and heparin were found within polyp stroma (24). Histamine, in comparison to serum levels, was found in 100- to 1000-fold concentrations within nasal polyps (2, 11).

## Cytokines

Interleukin (IL)-1 is regularly found in nasal polyps (45). Data regarding IL-3 are contradictory; in some studies, IL-3 was found either not at all or only intermittently at low concentrations (45, 46). Other studies regularly found IL-3 within polyp stroma (47). In most cases, IL-4 was inconsistently detected and seemed to be of no importance in nasal polyps (45, 48). Findings on IL-5 are discussed later. Concentrations of IL-6 and IL-10 in patients suffering from nasal polyps did not differ from controls (46). IL-8 could not be detected by Bachert et al. (46), although it was regularly found by others (45, 49).

The concentration of RANTES in polyp stroma has also been subject to contradictory findings. Some studies (46) could not detect any differences from controls, whereas others could regularly detect RANTES within the polyp stroma (50, 52) or even found increased levels of RANTES mRNA and protein (53, 55).

Interferon-gamma (IFN- $\gamma$ ) was detected in eosinophils, in the seromucous glands, and within the epithelium of nasal polyps. Increased levels of IFN- $\gamma$  were found in patients suffering from recurrent nasal polyps (56, 57).

## Growth factors

TNF- $\alpha$  and TNF- $\beta$  were regularly detected within nasal polyps (45). Eosinophils were considered the main source of TNF (41, 58, 59). Other studies (46) could not find significant differences in TNF concentrations from controls.

Increased levels of GM-CSF mRNA and protein were found in nasal polyps (53, 60). Eosinophils were considered a potential source of GM-CSF (61). Other studies (45, 46) either did not encounter GM-CSF, or found it only intermittently.

Activated macrophages or eosinophils were proposed as cellular sources of PDGF (62, 63).

VPF/VEGF, insulin-like growth factor I, and stem cell factor were also described in nasal polyps (64, 66).

## Adhesion molecules

Increased levels of VCAM-1 were found in nasal polyps (50, 60). ICAM-1 levels in nasal secretion were not found to be increased compared to controls or to allergic patients (9). E- and P-selectin were found within nasal polyps (50, 67).

## Other mediators

Increased levels of IgA and IgE were found within nasal polyps (2, 11, 56, 68). In the nasal secretion of nonallergic patients suffering from nasal polyposis, we found significantly increased levels of IgE compared to controls. These levels were as high as IgE levels in the nasal secretion of allergic patients without nasal polyps (9).

Elevated concentrations of substance P were found by Drake-Lee et al. (69); these findings were not confirmed in other publications (70).

Inducible NOS was found in nasal polyps as well (71). At cellular levels, increased numbers of CD8+ T cells were described in nasal polyps (7, 19).

## Eosinophilia

Eosinophilia, found in 80–90% of all cases, is the main histologic characteristic of nasal polyps (2, 38). Neutrophils predominate only when polyps arise in combination with CF, primary ciliary dyskinesia syndrome, or Young's syndrome.

In eosinophilic illnesses such as bronchial asthma, the degree of eosinophilia correlates with the intensity of the illness (72, 73), bronchial hyperresponsiveness (74), and response to glucocorticoids (75, 76). The correlation between the degree of eosinophilia and the glucocorticoid response is linked to glucocorticoid receptors on the human eosinophils. Inhibitory effects on the survival of eosinophils are thought to be transmitted via these receptors (25). Eosinophils are known to damage directly the epithelium of the upper and lower respiratory tract (19). The granules of eosinophils contain toxic products. These toxic substances trigger effects resulting in ciliostasis, lysis of epithelium, and nerve damage. Chronic inflammation, dyscrinism, and restriction of bronchial responsiveness follow (77). The contents of these granules include vasoactive substances, chemotactic factors, LTC, PAF, MBE, ECP, and eosinophilic peroxidases (25, 46). Specific granule protein, LTC<sub>4</sub>, and PAF are held to be responsible for the observed hyperresponsiveness of nasal mucosa and swelling (78). Furthermore, eosinophils are known to stimulate collagen synthesis (61).

There are several histologic markers of eosinophils. BMK<sub>13</sub> and EG<sub>1</sub> constitute paneosinophilic markers. BMK<sub>13</sub> is known to detect MBP, whereas EG<sub>1</sub> stains secreted and stored ECP within the granules of eosinophils. Therefore, BMK<sub>13</sub> and EG<sub>1</sub> can detect resting eosinophils (25, 79).

Activated eosinophils appear hypodense in light microscopy. They are more toxic, contain less MBP, and possess smaller granules. Their chemotactic response to PAF and their oxygen demand are higher than in resting eosinophils (25). EG<sub>2</sub> has been proposed as a specific marker for activated eosinophils. It stains secreted ECP only (25, 79).

Activated, degranulated, and EG<sub>2</sub>-positive eosinophils predominate in polyp stroma (46, 79, 80). Significantly higher numbers of activated eosinophils were found in patients suffering from a combination of bronchial asthma and nasal polyps than in nonasthmatic patients suffering from nasal polyps. Correlation of this data with eosinophil counts of the peripheral circulation has been noted. Differences in the number of activated eosinophils between allergic and nonallergic patients with nasal polyps could not be detected (25).

## Stimuli of eosinophilia

There are numerous triggers of eosinophilia. IL-1 enhances the expression of adhesion molecules on endothelial cells. This results in an increased transendothelial migration of

eosinophils and neutrophils into the tissues (45). As described above, IL-1 was regularly found in nasal polyps (45), but the question of whether it plays a relevant role in eosinophilia has not been answered.

IL-3, GM-CSF, and IL-5 are known as major factors in the survival of human eosinophils (46, 81). As mentioned above, some authors (45, 46) could only inconstantly detect IL-3 in nasal polyps and excluded the possibility of its playing a relevant role in eosinophilia. Others established a positive correlation between IL-3-mRNA levels and the number of eosinophils in nasal polyps (47, 57) or determined a positive correlation between IL-3 and the degree of activation of eosinophils (82, 83). Thus, the role of IL-3 in the eosinophilia of nasal polyps remains unclear.

IL-4, a typical Th<sub>2</sub> interleukin, has been established as essential for the synthesis of IgE. The corresponding findings of several other authors confirm that IL-4 does not play a relevant role in the eosinophilia of nasal polyposis (45, 48).

IL-5 plays a key role in eosinophilia. It mediates the activation and selective migration of eosinophils from the peripheral circulation into the tissues (46). It is also known to constitute a major survival factor for human eosinophils (46, 81). Eosinophils are the only human leukocytes expressing receptors specific for IL-5, a fact which leads to the conclusion that IL-5 is a key factor in human eosinophilia (84, 85). The relevance of IL-5 to nasal polyposis is discussed below.

IL-8 is proposed as a relevant chemotactic factor for neutrophils and, under certain circumstances, for eosinophils (45). It can be regularly found in nasal polyps (45, 49). The relevance of IL-8 to eosinophilia is still unclear.

The chemokine RANTES is known to mediate the recruitment of eosinophils and lymphocytes (52) via its chemotactic properties for lymphocytes, macrophages, and eosinophils (51, 60). No correlation between the number of eosinophils and the intensity of RANTES staining could be found in nasal polyps (50), and no differences in RANTES levels from those of controls have been described (46). Hamilos et al., however (53), found increased levels of RANTES mRNA and protein in nasal polyps. At present, the relevance of RANTES to the eosinophilia of nasal polyps is still under scrutiny.

GM-CSF, in combination with IL-3 and IL-5, constitutes a major survival factor for human eosinophils (46, 81). A positive correlation between the number of eosinophils and GM-CSF-mRNA levels in nasal polyps has been established (47, 57). Increased levels of GM-CSF mRNA and protein were found regardless of whether the patients also suffered from allergies or not (53). Thirty percent of the eosinophils

were found to produce GM-CSF; the GM-CSF levels correlated to the degree of eosinophilic activation (82, 83). Other publications (46) have dismissed the relevance of GM-CSF in eosinophilia. Simon (45) did not detect GM-CSF in nasal polyps at all. Although the findings point strongly to the relevance of GM-CSF to the eosinophilia of nasal polyposis, conflicting data do not allow a definite conclusion.

VCAM-1 selectively mediates the migration of eosinophils and mononuclear cells from the peripheral circulation into the tissues (50). VCAM-1 is upregulated by TNF- $\alpha$ , IL-1, IL-13, and RANTES (60). Elevated levels of VCAM-1 and a positive correlation between VCAM-1 and the number of eosinophils have been determined by Beck et al. (50). Therefore, VCAM-1 seems to play a relevant role in the tissue eosinophilia of nasal polyps.

As noted above, TNF- $\alpha$  upregulates the expression of adhesion molecules such as VCAM-1 and indirectly promotes the transendothelial migration of eosinophils. TNF- $\alpha$  has been regularly found in nasal polyps (45) and, accordingly, seems to play a relevant role in the eosinophilia of nasal polyposis.

## Causes of tissue eosinophilia

As we mentioned, there are several factors relevant to the recruitment of eosinophils in nasal polyps from the peripheral circulation. It is questionable whether recruitment alone can explain tissue eosinophilia. Therefore, additional factors must be considered: IL-3, IL-5, and GM-CSF are known to be the main survival factors for human eosinophils. The apoptosis of eosinophils in nasal polyps is regulated by these proteins.

## Delayed apoptosis of eosinophils

Delayed apoptosis as a possible factor in tissue eosinophilia in eosinophilic diseases such as bronchial asthma, chronic-allergic diseases, or nasal polyposis is an increasing focus of research. Usually, apoptosis is mediated via activation of *Fas* receptors, which typically results in an activation of ICE (IL-1 $\beta$ -converting-enzyme) proteases.

In human eosinophils, apoptosis shows some differences from animal models: an activation of tyrosin-kinases was found in murine and human eosinophil apoptosis, leading to protein activation that initiated cell death. Furthermore, donors suffering from eosinophilic diseases often lack

functioning *Fas* receptors of their eosinophils (45, 86). Investigations of chronic-allergic inflammation, an illness characterized by tissue eosinophilia as well, often revealed a resistance to *Fas*-mediated apoptosis (87) and a blockade of apoptosis by autocrine or paracrine survival factors. In such cases, activated T cells, producing cytokines such as IL-3, IL-5, and GM-CSF, can be determined. Furthermore, somatic abnormalities of the *Fas* receptors of these activated T cells were established, sufficiently preventing apoptosis of these clones (84). An overproduction of eosinophilic survival factors caused a delay in apoptosis of eosinophils and resulted in tissue eosinophilia (45, 88, 89).

## Delayed apoptosis of eosinophils in nasal polyps

A delayed apoptosis of eosinophils within the stroma of nasal polyps has been determined (45, 48, 86). Apoptosis was induced *ex vivo* by anti-IL-5 antibodies in cultured human epithelial cells of nasal polyps. A reduction in the number of eosinophils resulted (45, 48, 86).

A detailed description of the findings of Simon and coworkers follows (45, 48, 86, 90). In controls, eosinophils disappear regularly after 3 days in culture – this is similar to the survival period of eosinophils within the peripheral circulation. In a cell culture of nasal polyps, apoptosis of eosinophils did not take place within the first 12 days. IL-5 mRNA and protein were regularly found, whereas other eosinophil survival factors, such as IL-3 or GM-CSF, were detected only inconstantly. An induction of apoptosis was observed after the addition of anti-IL-5 antibodies and caused a decrease in the number of eosinophils.

## Eosinophil survival factors: IL-3, IL-5, and GM-CSF

IL-3, IL-5, and GM-CSF are known as survival factors for human eosinophils (46, 81). Their cellular receptors are formed out of two subunits. The  $\alpha$ -chain codes specific for IL-3, IL-5, or GM-CSF, whereas the  $\beta$ -chain is identical in each of the three receptors. The antiapoptotic cascade is initiated via activation of the  $\beta$ -chain. Simon and coworkers (45, 48, 86, 90) suggested the possibility of an antiapoptotic pathway with the tyrosin kinases Lyn and Syk that are physically linked to the  $\beta$ -chain and form a signal-transducing complex. Activation of the  $\beta$ -chain results in phosphorylation of tyrosine (Lyn, Syk) and in the expression

of antiapoptotic genes such as Bcl-2 in activation of the JAK2-STAT-1 pathway, inhibiting apoptosis. Both the kinases Lyn and Syk were determined to be essential parts within the antiapoptotic pathway induced by IL-5 and GM-CSF in human eosinophils.

TGF- $\beta$  is regarded as a counterpart in the  $\beta$ -chain-mediated effects of IL-3, IL-5, and GM-CSF. A TGF- $\beta$ -induced inhibition of the cytokine-initiated activation of the antiapoptotic pathway and a TGF- $\beta$ -induced inhibition of the survival of eosinophils have been demonstrated (91).

Possible therapeutic targets for induction of eosinophil apoptosis have been suggested (45). The induction of apoptosis could be initiated by inducing apoptosis in T-cell clones producing these eosinophilic survival factors; or by neutralizing of these survival factors by anticytokine antibodies or by cytokine receptor antagonists. Furthermore, apoptosis should be induced by blocking signal transducing by inhibition of tyrosine kinases. Moreover, a direct activation of eosinophil apoptosis via local activation of the *Fas* receptor by anti-*Fas* antibodies or recombinant *Fas* ligands has been proposed.

## Interleukin-5 (IL-5)

### IL-5 and eosinophilia

IL-5 is mainly produced by Th2 cells; however, mast cells and eosinophils are also proposed sources of IL-5 (77). Among the influences of IL-5 on eosinophils is the fact that it is essential for their differentiation and proliferation influences in bone marrow (92). Aside from its effects on eosinophil precursors, IL-5 affects mature eosinophils as well: it acts as a selective chemotactic on eosinophils, activates eosinophils, and promotes the survival of eosinophils (93, 97). In addition, its action is generally proinflammatory and promotes the degranulation of eosinophils in reaction to specific stimuli (77).

The expression of the adhesion molecules VCAM-1 and ICAM-1 in nasal mucosa is augmented by IL-5. Not only does IL-5 produce direct chemotactic effects in eosinophils, but it also promotes the recruitment of eosinophils from the peripheral circulation into the tissues (92, 98).

Eosinophils are the only human leukocytes with receptors specific for IL-5, pointing to this cytokine's importance in the pathogenesis of eosinophilia (84, 85). IL-5 is also one of the essential survival factors for human eosinophils as described above (46, 81).

### IL-5 in allergic rhinitis

The concentration of IL-5 in nasal secretion correlates significantly with the intensity of symptoms (99). The concentration of IL-5 and IL-5 gene expression in nasal secretion peaks after 6 h of specific antigen provocation and, significantly, correlates with an increased number of eosinophils (100, 102). After treatment with glucocorticoids, a reduced number of eosinophils was observed (77).

### IL-5 in nasal polyposis

There are numerous reports (46, 48, 103, 107) of significantly increased levels of IL-5 within the stroma of patients suffering from nasal polyps; a mean concentration of 11.45 pg/ml was reported. No differences between nonallergic and allergic patients suffering from nasal polyps could be found, compared to increased levels in association with bronchial asthma (46, 104). Statements of nonelevated levels of IL-5, as presented by Hamilos et al. in older publications (47), have recently been revised (53).

IL-5 concentration in the nasal secretion of nonallergic patients suffering from nasal polyps reaches similar levels in allergic patients without nasal polyps. These levels are significantly higher than those of the controls (9).

As already pointed out, IL-5 constitutes, together with IL-3 and GM-CSF, a main survival factor for human eosinophils (46, 81). In nasal polyposis, however, only IL-5 is of relevance to tissue eosinophilia (46).

Th2 cells are the main cellular source for IL-5. A strong correlation between IL-5 immunostaining and the number of T cells was reported (53). Apart from Th2 cells, eosinophils are considered an additional source of IL-5. Sixty-nine percent of IL-5-positive cells within the stroma of nasal polyps could be identified as eosinophils (46). Most of these eosinophils were activated (EG2 positive) (104).

### Intranasal administered recombinant human IL-5

The intranasal application of recombinant human IL-5 in patients suffering from allergic rhinitis induces accumulation and activation of eosinophils within the nasal mucosa (92, 108). The number of eosinophils and levels of ECP increase significantly, as do the number of epithelial cells and levels of sIgA and IgA. An increased response to histamine was also reported (108). In addition to the observed accumulation of eosinophils within the epithelium and lamina propria, an increase of eosinophils within supplying vessels was observed. This increase underlines

the importance of IL-5 in the recruitment of eosinophils from the peripheral circulation. Neutrophils did not seem to be affected (92).

### Anti-IL-5 antibodies in animal models

#### Mice

Migration of eosinophils from the bone-marrow trough of the systemic circulation into the lungs and bronchial lumen after antigen challenge appears to be mediated by IL-5, since these effects are inhibited by the prophylactic application of anti-IL-5 antibodies (109, 110). The pulmonary infiltration of eosinophils in sensitized mice could also be prevented by a prophylactic application of anti-IL-5 antibodies (111, 113). The effects of a single, prophylactic application of anti-IL-5 antibodies lasted as long as 5 days (110). Other authors have confirmed these prolonged effects (114) and even described effects lasting over several weeks (115). A persistence of these anti-IL-5 antibodies within the peripheral circulation and a “honeymoon period” after the initial suppression of the inflammation were considered possible causes of the observed prolonged effects.

The application of anti-IL-5 antibodies effectively prevented eosinophilia in mice without negative effects on the immune protection against parasites (116, 119).

#### IL-5 knockout mice

Bronchial or pulmonary eosinophilia, damage of the lung, and hyperresponsiveness of the lung could not be detected after antigen challenge in IL-5 knockout mice. The normal sequence after antigen challenge was observed after the reassembly of the IL-5 gene (120). Other than their low eosinophil counts, IL-5 knockout mice develop normally and have normal humoral and cellular immune responses. They do not develop eosinophilia. No increased rate of infection was observed after challenge with helminths (121).

#### Guinea pig and monkey

The antigen-induced cellular infiltration of eosinophils in sensitized guinea pigs or allergic monkeys can be prevented by a prophylactic application of anti-IL-5 antibodies (114, 122).

### Suggested ways to block IL-5-mediated effects

#### Glucocorticoids and cyclosporine

Glucocorticoids and, to a lesser degree, cyclosporine effectively block the synthesis of IL-5 (77, 123). The effects

of glucocorticoids include reduction in the number and activation of eosinophils and mast cells, impairment of chemotaxis and adherence of eosinophils (and basophils), impairment of the differentiation of eosinophils, inhibition of mediator release of mast cells and basophils, and reduction in the number and activation of T cells (79, 124).

#### Soluble IL-5 receptor

The application of a soluble IL-5 receptor results in a blockage of IL-5-mediated effects (125, 126).

#### Mutated IL-5 protein without biologic effects

The application of mutated IL-5 protein without biologic properties could, at least in theory, also block IL-5-mediated effects.

#### Antibodies against IL-5 or against the $\beta$ -chain of the IL-3, IL-5, and GM-CSF receptor

As already pointed out, there are several reports demonstrating sufficient, long-lasting, safe, and selective effects of anti-IL-5 antibody therapy in animal models without major side-effects. According to Danzig & Cuss, evidence “strongly suggests that anti-IL-5 therapy may be an effective, safe, and novel way of treating human asthma and perhaps other eosinophilic diseases” (77).

### Antibodies in therapy – possible hazards

There are possible risks that have to be considered before a therapeutic application of antibodies to man. The main risk is the induction of an immune response to these antibodies. This problem occurs not only when administering antibodies originating from animals – even the application of human antibodies involves the risk of inducing, for example, an anti-idiotypic immune response. These immune responses range from an inhibition of the therapeutic effects to serum disease or anaphylaxis (even after the first dose) (77, 127). Therapeutic studies report a general incidence of immune responses of 0–30% (77). This incidence could be diminished by reducing murine components or by applying human antibodies (77, 127).

Locally administered doses of anti-IL-5 antibodies should be less toxic than systemically applied doses of antibodies, and lower concentrations should be sufficient to achieve significant therapeutic effects.

## Summary

Eosinophilia is the main characteristic of nasal polyps. Eosinophils damage the tissue and promote the inflammatory process. In tissue eosinophilia of nasal polyposis, IL-5 plays a pivotal role: it is essential for the proliferation and differentiation of eosinophil precursors and has numerous effects on mature eosinophils. Its action is chemotactic on eosinophils and promotes the migration of eosinophils from the peripheral circulation into the tissues. Furthermore, it activates eosinophils and prolongs eosinophilic survival via inhibition of apoptosis.

The application of anti-IL-5 antibodies in animal models sufficiently prevents IL-5-mediated effects on eosinophils

over a prolonged period without causing major side-effects. Therefore, the therapeutic application of locally administered anti-IL-5 antibodies or antibodies against the  $\beta$ -chain of the IL-3, IL-5, and GM-CSF receptor to patients suffering from nasal polyposis seems to be an effective and safe approach for controlling the disease and/or reducing rates of recurrence.

This treatment could also be used as a model to treat other eosinophil diseases such as bronchial asthma or chronic allergies. The local application of these antibodies promises to be less toxic than a systemic application and should give essential information for a future systemic application in other eosinophilic diseases; therefore, it is of interest not only ENT surgeons.

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