REVIEW

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An update on the impact of *Staphylococcus aureus* enterotoxins in chronic sinusitis with nasal polyposis*

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SUMMARY

Nasal polyps in adults, characterized by abundant eosinophils, local overproduction of immunoglobulin E, and often associated with asthma, have been appreciated as an eosinophilic inflammation, potentially of allergic origin, but unrelated to a bacterial impact. Evidence accumulates, however, that Staphylococcus aureus colonizes chronic rhinosinusitis with, but not without polyps, with significantly increased prevalence. The germs release enterotoxins, which act as superantigens and induce a topical multiclonal IgE-formation as well as a severe, possibly steroid-insensitive eosinophilic inflammation. Recently, S. aureus could be demonstrated to reside intraepithelially, and potentially to release superantigens into the tissue from within the epithelial cells. An immune defect, either in the innate or adaptive immunity, might be responsible for this phenomenon. Follicle-like structures and lymphocyte accumulations, specifically binding enterotoxins, can be found within the polyp tissues, giving rise to local IgE formation.

The superantigen-induced immune response also leads to a modulation of the severity of the eosinophilic inflammation, and may be linked to lower airway co-morbidity in polyp patients. Interestingly, IgE antibodies to enterotoxins can be found in the majority of aspirin-sensitive polyp tissues, associated with a substantial increase in ECP and IL-5. The possible role of S. aureus enterotoxins in polyp disease in Europe, the US and Asia has meanwhile been supported by several studies, demonstrating the presence of IgE antibodies to enterotoxins and inflammatory consequences in nasal polyp tissue.

First studies also point to an involvement of S. aureus derived enterotoxins in lower airway disease, such as severe asthma and exacerbated COPD, clearly suggesting a clinical need for diagnosis and treatment of the germ and its related effects. Therapeutic approaches are so far empirical, and need further study, also serving to proof the clinical relevance of the concept.

Key words: Staphylococcus aureus, intracellular, enterotoxins, superantigens, nasal polyps, chronic sinusitis, asthma, COPD, aspirin sensitivity, IgE, steroid insensitivity, ECP

LIST OF ABBREVIATIONS: AD, atopic dermatitis; ASNP, aspirin-sensitive nasal polyp; ATNP, aspirin-tolerant nasal polyp; BAL, broncho-alveolar lavage; CRS, chronic rhinosinusitis; COPD, chronic obstructive pulmonary disease; DBPCR, double-blind placebo-controlled randomized; ECP, Eosinophil cationic protein; FEV1, forced expiratory volume in one second; FnBPs, fibronectin-binding proteins; Hsp60, heat shock protein 60; IgE, immunoglobulin E; IL-5, interleukin-5; LT, Leukotriene; MMR, Macrophage mannose receptor; NP, Nasal polyposis; SCORAD, the Severity Scoring in AD; SCV, Small-Colony Variants of *S. aureus*; SE, *Staphylococcus aureus* enterotoxins; SE A-E, *Staphylococcal* enterotoxin A-E; SE-IgE, IgE antibodies against SE; SEM, *Staphylococcal* enterotoxin M; SEO, *Staphylococcal* enterotoxin O; *S. aureus, Staphylococcus aureus*; TCR, T-cell Receptor; TSST-1, Toxic shock syndrome toxin-1; PBMCs, peripheral blood mononuclear cells; PGE_2, prostaglandin E_2; PHA, phytohemaglutinine

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INTRODUCTION

Nasal polyposis (NP) is characterized by abundant eosinophils, T-cell activation, overproduction of immunoglobulin E (IgE), and originally was thought to represent an allergic disease [1-5]. In western countries, more than 70% of polyps show tissue eosinophilia, and increased concentrations of interleukin (IL)-5 and eotaxin, inducing eosinophil chemotaxis, migration, activation and prolonged survival [2,3]. Recent evidence accumulates, however, that *S. aureus* enterotoxins (SE), acting as superantigens, induce a substantial inflammatory reaction in a large subgroup of NP, and strongly modify the disease [3].

About 25% of the population is permanent carrier of *S. aureus* in the nostrils, and approximately 20% of all human *Staphylococcal* infections are autogenous [6]. Although the pathogenicity of *S. aureus* is closely correlated to the production of coagulase enzymes, these organisms also contain a number of cellular antigens and produce a variety of toxins with superantigenic properties [7,8]. The classical *S. aureus* enterotoxins (SE) comprise SE A-E and TSST-1 (Toxic shock syndrome toxin-1), however, other enterotoxins have been described recently, derived from the egc-gene locus [9]; these seem to be of relevance, as they frequently are produced by nasal *S. aureus*, and partially are unrelated to the production of classical enterotoxins (T. van Zele, unpublished). *Staphylococcal* enterotoxins, as well as molecules derived from *Streptococcus pyogenes* [10] and some viruses [11,12], are able to activate T-cells via the T-cell receptor (TCR)-MHC class II-complex independent from the antigen-specific groove by binding to the variable beta-chain of the TCR. The susceptibility of a T-cell to superantigens therefore is dependent on the usage of a specific beta-chain repertoire, possibly leading to the activation of abundant T-cells in a given tissue (normally, far less than 1% of T-cells are activated by a specific antigen). Another recently described possibility of modifying the response to superantigens is based on the finding that HLA-DQ polymorphisms may alter the binding of superantigens to the MHC class II complex [13]. Thus, the resulting response of a T-cell population in a given tissue is dependent on many factors, such as production of and exposure to *S. aureus* enterotoxins, the intactness of the epithelial barrier, as well as the specific composition of TCRs and MHC class II complexes on immune cells. Once activated, T-cells would produce interleukins including IL-4, IL-5, IL-13, eotaxin and many others, which would lead to a severe eosinophilic inflammation and local IgE-production. Other direct actions of superantigens on B-cells, epithelial cells, eosinophils etc. have been described, which are summarized in a recent review [14]. All of these actions add to the enormous inflammatory potential of *S. aureus* derived and other superantigens.

The finding of IgE-antibodies to *S. aureus* enterotoxins SE A and SE B in nasal polyp tissue homogenates [3] for the first time indicated that these superantigens could be involved in the pathogenesis of nasal polyposis. Investigating tissue homogenates, we sought to determine the association between total and specific IgE to a variety of allergens in polyp and control samples, and to markers of eosinophilic inflammation. The concentrations of total IgE, IL-5, eotaxin, eosinophil cationic protein (ECP), the cys-leukotrienes (LT), and the soluble low-affinity IgE-receptor (CD23) were significantly higher in polyp tissue compared to controls. Total IgE was significantly correlated to IL-5, ECP, LTC4/D4/E4, and sCD23, and to the number of eosinophils. An important subgroup of those polyp patients demonstrated a multiclonal IgE formation, including IgE to *S. aureus* enterotoxins, a high total IgE level, and a high prevalence of asthma. These studies suggested that bacterial superantigens could induce IgE-synthesis in nasal polyps and impact the degree of eosinophilic inflammation [3,15].

We here summarize the evidence gathered so far, from our and other groups, and provide an outlook on the possible clinical implications for the management and therapy of nasal polyposis.

S. AUREUS COLONIZATION AND IMMUNE RESPONSE TO SE'S IS INCREASED IN NASAL POLYPOSIS

S. aureus frequently colonizes the nostrils in healthy subjects, and can be found in acute and chronic rhinosinusitis [16]. However, this germ has never been identified as a prominent player in chronic sinus disease without acute exacerbation, and studies in NP have not been performed. We recently reported an increased colonization rate of *S. aureus* in nasal polyps, but not in chronic rhinosinusitis (CRS) without polyps [17], indicating that NP and CRS might be different disease entities with distinct underlying pathomechanisms (Figure 1). Colonization with *S. aureus* was present in 63.6% of subjects with polyps, with rates as high as 66.7% and 87.5% in the subgroups with asthma and aspirin sensitivity, which were significantly higher than in controls and subjects with CRS (33.3% and 27.3%, respectively). Furthermore, repeated swabbing of the middle meatus in 8 subjects with polyps suggested long-term colonization with *S. aureus*. IgE antibodies to *S. aureus* enterotoxins, using a combination of different enterotoxins in a screening assay, were present in 27.8% in polyp samples, with rates as high as 53.8% and 80% in the subgroups with asthma and aspirin sensitivity, com-

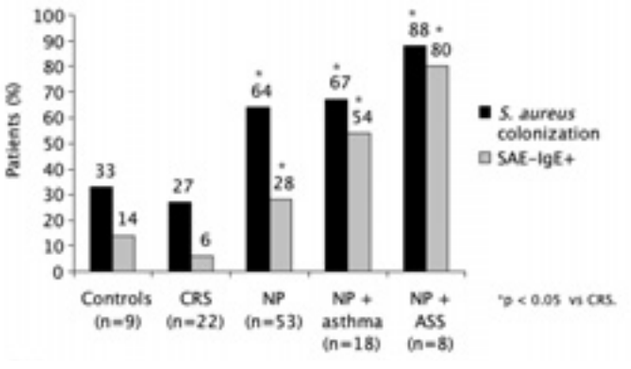

Figure 1. *S. aureus* colonization and IgE antibodies to *S. aureus* enterotoxin mix in mucosal tissue.

pared to 15% in controls and 6% in subjects with CRS, respectively. The concentration of ECP, reflecting the eosinophilic inflammation, was significantly increased in polyp samples with the presence of IgE antibodies to enterotoxins versus samples without IgE, suggesting a strong inflammatory effect of superantigens. In subjects with NPs and co-morbid asthma or aspirin sensitivity, rates of colonization and IgE response in nasal tissue homogenates were further increased, paralleled by increases of ECP and total IgE. These figures indicate that there is a strong relation between *S. aureus* colonization and tissue immune response to enterotoxins in nasal polyps, which even may be reflected in lower airway co-morbidity.

Comparable rates of colonization with *S. aureus* (71%) and IgE antibody formation (50%) to superantigens were found in another polyp study, with low rates in control subjects (25% and 0%, respectively), confirming our first results [18]. Colonization rates always exceeded those of IgE immune response to *S. aureus* enterotoxins, indicating that colonization may not necessarily lead to the production or contact of superantigens with the immune system.

EVIDENCE FOR INTRAEPITHELIAL GROWTH OF *S. AUREUS*

Until now, *S. aureus* has been regarded as non-invasive extracellular pathogen [19]. However, recent findings demonstrate the ability of this germ to invade non-phagocyting eukaryotic cells, and to possibly persist there for weeks. *S. aureus* Small-Colony Variants (SCV) are a naturally occurring slowly growing subpopulation which was recently related to chronic recurrent antibiotic-resistant infections such as cystic fibrosis [20,21]. It has been demonstrated that *S. aureus* invades cultured cells of non-professional phagocytes and cell lines [22,23], as well as human respiratory epithelial cells [24-26]. Analysis of invaded cultured cells by electron microscopy revealed *S. aureus* in vacuoles within the airway epithelium [24,27]. The interaction between *S. aureus* and epithelial cells has been proposed to occur through binding of fibronectin-binding proteins (FnBPs) on germs to fibronectin, β1-integrines and heat shock protein 60 (Hsp60) [25,28,29]. The ability to be internalized and survive within host cells may explain the refraction of polyp disease to antibiotic treatment, which represents a hallmark of polyposis, as well as the chronicity of disease and recurrence, months and even years after apparently successful therapy. Antibiotics commonly used for the management of *S. aureus* infections appear to create a niche for invasive intracellular *S. aureus* [30].

We recently used immunohistochemistry to demonstrate presence of *S. aureus* and production of SEB in samples from polyps (Figure 2). Intraepithelial staining for *S. aureus* was found in a substantial subgroup of polyps, with affected and unaffected areas coexisting in the same samples (J. Patou, unpublished). SEB could be co-localized to the intracellular *Staphylococcus*, indicating the potential of releasing this enterotoxin into the tissue. Further studies need to address the issues of germ survival and ongoing enterotoxin production in intraepithelial *S. aureus*. Apoptotic epithelial cells with their contents, and *S. aureus* which crosses the basal membrane, would be taken up by macrophages, which have been shown to be prevalent in increased numbers in nasal polyps vs. controls [31]. These macrophages in nasal polyp tissue have been characterized as CD 68+, Macrophage mannose receptor (MMR)+, CD 163+, RFD7+ phagocyting macrophages, which characterize a mature phenotype of macrophages. Surprisingly, there was a significant lack of staining for *S. aureus* in macrophages in the lamina propria in polyp tissues compared to controls. These new data suggest a reduced capacity of these macrophages to phagocyte *S. aureus*, which needs further functional investigation. Of interest, the lack of defense against *S. aureus* seems to give rise to a local immune response to *Staphylococcal* enterotoxins, as measured by increased IgE antibodies to enterotoxins, total IgE, ECP and IL-5 vs. controls in this patient group. In the skin, another possible deficiency in innate immunity, namely the lack of defensines, has been proposed [32], which we could not confirm in our studies on nasal polyps [33]. Furthermore, a deficit in IgG_2 antibodies against enterotoxin C1 has been described recently, the clinical relevance of which currently is unclear [34] and has to be studied also in polyps. However, if confirmed, this finding could indicate a deficiency not only in the innate, but also in the adaptive immune regulation, which could predispose to develop *Staphylococcal* superantigen driven disease.

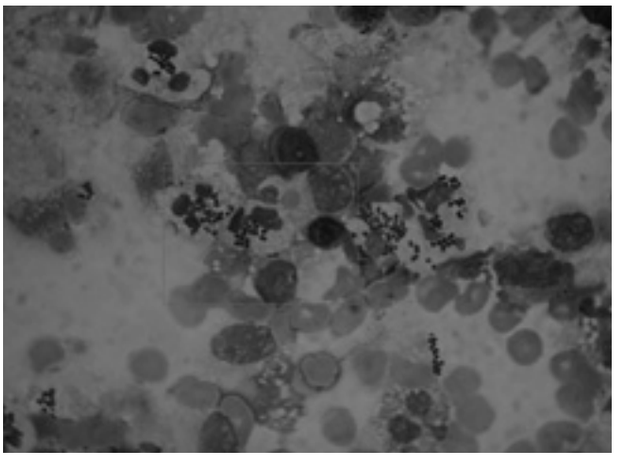

Figure 2. Intracellular *S. aureus* in epithelial cells of nasal polyps.

ORGANIZATION OF SECONDARY LYMPHOID TISSUE AND EVIDENCE FOR LOCAL IgE FORMATION TO *S. AUREUS* ENTEROTOXINS

When nasal polyps were analyzed for T- and B-lymphocytes and IgE by immuno- histochemistry, follicular structures were found in 25% of the samples, and diffuse lymphoid accumulations were seen in all NP samples [18]. Follicle-like structures are composed of T- and B-lymphocytes, and stain positive for IgE and the low affinity IgE receptor, whereas the high-affinity

receptor is found outside the follicle only. Plasma cells expressing CD38 are prominent in the lymphoid accumulations, which also stain positive for IgE, CD3, FcεRI, but not for CD23. These lymphocyte accumulations therefore may be considered to develop from follicle-like structures, with B-cells maturing into IgE-producing plasma cells. Interestingly, we demonstrated binding of biotinylated SEA to follicular structures and lymphoid accumulations in polyp tissue. The specificity of the SE binding was confirmed by staining with an excess of non-biotinylated SEA to biotinylated SEA, which completely blocked the signal. Furthermore, no follicular structures or SE staining were found in control tissue. These data suggest an organization of secondary lymphoid tissue with polyclonal B-cell activation in nasal polyps due to chronic microbial colonization and stimulation by enterotoxins, which is likely to be the cause of IgE switch and formation.

There is increasing evidence that SEs can directly affect the frequency and activation of the B cell repertoire. Functional studies in B-cells have shown that *S. aureus* protein A induces proliferation of these cells [35]. Studies with TSST-1 indicated that *Staphylococcal* superantigens may play an important role in the modulation of allergic disease, since they may augment isotype switching and synthesis of IgE, both *in vitro* [36] and *in vivo*, in a SCID mouse model [37]. Although TSST-1-induced activation of B-cells *in vitro* is indirect and dependent on increased expression of CD40 ligand on T-cells, a more recent study has provided evidence for also a direct effect by demonstrating TSST-1-induced expression on B-cells of B7.2 [38], a molecule that has been shown to enhance Th2 responses and to be involved in IgE regulation. In mucosal tissues of hay fever and asthma patients, mRNA for the ε-chain of IgE was found in a significant proportion of B cells using *in situ* hybridisation [39-42], supporting the hypothesis of a truly local IgE synthesis in the airway mucosa. Pilot studies on the expression of co-stimulatory signals such as CD40/CD40 ligand and CD28/B7 in lymphocytes of nasal polyps support this notion (T. van Zele, unpublished data), and studies on local IgE switching events are currently performed [43].

Nasal culture of the middle meatus demonstrated an increased staphylococcal colonization in polyp patients vs. controls, as discussed before [17], associated with a significant increase in tissue concentrations of IgE, albumin, and eosinophil counts. Total IgE and IgE-antibody concentrations to enterotoxins were in all cases higher in tissue compared to serum, but SE-specific IgE-antibodies may be detected in the serum of polyp patients [15], esp. when asthma coexists. The IgE/albumin ratios in polyp tissue and in serum were dissociated, again indicating that tissue IgE is rather the result of a local IgE production than of extravasation. Furthermore, IgE antibodies in polyp tissue only showed a partial relation to IgE antibodies in serum and to skin prick test results. In a substantial subgroup of patients, the typical pattern of IgE expression in polyp tissue was found: a polyclonal type of IgE expression with IgE antibodies to common aeroallergens and a high level of total IgE. These findings resemble those in atopic dermatitis, where colonization of the inflamed skin with *S. aureus* clearly contributes to the high IgE levels in serum and to the severity of the disease [44].

THE RELATION OF SES TO ASPIRIN SENSITIVITY

From the first study in patients with local IgE against *Staphylococcal* enterotoxins [3] it appeared that the highest IgE concentrations were obtained from samples of aspirin sensitive subjects. We therefore extended our observations in this non-allergic, but severely inflamed subgroup of patients, who also suffered from asthma. Forty subjects with nasal polyposis (NP) from Poland were classified as aspirin-sensitive (n = 13, ASNP) or aspirin-tolerant (n = 27, ATNP) based on a bronchial aspirin challenge test [45]. Homogenates prepared from nasal polyp tissue and inferior nasal turbinates from healthy subjects were analyzed for concentrations of IL-5, ECP, total and IgE to a mix of SEs (A, C, TSST-1), a screening test which was developed in cooperation with SGO Johansson [46].

A significant increase in IL-5 concentrations, total IgE and IgE antibodies to SEs was observed in samples from supernatants in NP patients compared to controls, with levels of IgE to SEs correlating to IL-5 and ECP levels. Patients were further analyzed in two groups, with or without aspirin sensitivity (ASNP and ATNP, respectively). Concentrations of total IgE and IgE antibodies to a mix of SEs (SEA, SEC, TSST-1) showed significantly higher levels in ASNP patients compared to ATNP and control groups as well. Also, quantities of IL-5 and ECP were up-regulated in ASNP and differed significantly from ATNP and control subjects. These results confirmed that the immune response to SEs was linked to the up-regulation of eosinophilic inflammation, and suggested a possible link of SEs to aspirin sensitivity, which might be direct (SEs inducing superantigen) or indirect (via the severity of inflammation). Therefore, ASNP and ATNP patients were each divided in two subgroups, with and without SEs. Out of 13 patients with ASNP, 7 were SE(+) in comparison to 7 out of 27 in the ATNP group and none out of 12 subjects in the control group. Concentrations of inflammatory markers (IL-5 and ECP) did not differ between ASNP-SE(+) and SE(–) groups, but were up-regulated with respect to the control group. These observations rather suggested an indirect link between SEs and aspirin sensitivity.

Further investigations, comparing eicosanoid production and eosinophilic markers in chronic rhinosinusitis patients with and without nasal polyps, with nasal polyps and aspirin sensitivity, and finally in normal nasal mucosa from healthy subjects, showed that LTC_4S, 5-LO mRNA and $LTC_4/D_4/E_4$ concentrations increased with disease severity (per patient group) [47]. Other metabolites such as COX-2 and prostaglandinE_2 (PGE_2) significantly decreased with disease severity. IL-5 and ECP were increased in both groups of nasal polyp tissues compared to

controls and CRS, and correlated directly with $LTC_4/D_4/E_4$ and inversely with PGE_2 concentrations. These data confirmed the notion that changes of tissue eicosanoid metabolism do occur in chronic rhinosinusitis even in the absence of clinical aspirin sensitivity and appear to be related to severity of eosinophilic inflammation, with SEs being a strong modifier of local and systemic inflammation in nasal polyps.

Our findings were recently confirmed by Suh et al. [48], who studied IgE antibodies to SEs and eosinophilic markers in aspirin-sensitive and tolerant asthmatics with nasal polyps. These authors also found an increase in ECP, but not IL-5, between these groups, and significantly increased levels of IgE to SEs in aspirin-sensitive subjects. The authors also confirmed the relevance of the impact of SEs on nasal polyp disease in Korea, expanding on our European observations.

SE'S PROVIDING A LINK TO LOWER AIRWAY DISEASE

Until recently, there only was indirect evidence that SEs possibly could also impact lower airway disease unrelated to nasal polyposis, esp. in poorly controlled asthma. By studying the TCR -Vbeta repertoire of broncho-alveolar lavage (BAL) cells and peripheral blood mononuclear cells (PBMCs) from subjects with poorly controlled asthma (FEV1 <75%), subjects with well-controlled asthma, and control subjects, D. Leung and co-workers found a significantly higher expression of Vβ8(+) T cells in BAL fluid of poorly controlled asthmatics compared to the other groups. Increased Vβ8(+) BAL T cells were present in the CD4(+) and CD8(+) subsets, suggesting activation by SEs [49].

Experiments in mice to delineate the type of immune response triggered by superantigen exposure to the airway mucosa showed that a low dose of SEB could trigger an inflammatory response characterized by mucosal and airway recruitment of lymphocytes, eosinophils and neutrophils. These responses were associated with the development of increased airway responsiveness in SEB-treated mice, observed in IgE-high responder Balb/c as well as in IgE-low/intermediate responder C57Bl/6 mice. These results suggested that the local immune response following mucosal superantigen administration triggers a unique inflammatory response in the airways in mice, resembling many features of "intrinsic asthma" [50]. A similar experimental model is currently used to further elucidate the interaction between lower and upper airway *Staphylococcal* enterotoxin effects.

Also in humans, evidence for a direct impact of enterotoxins on lower airway disease is growing. Based on our previous findings, we used sensitive and highly specific screening tool, the SAE mix, to detect IgE to SAEs in serum of mild and severe asthmatics, classified by lung function and need for drug treatment, versus controls. IgE antibodies to SAE mix were found significantly more frequent in severe asthmatics (62%) versus controls (13%, p=0.01), and were linked to concentrations of IgE antibodies in serum, severity of eosinophilic inflammation (ECP in serum), and corticosteroid dependence [46]. Thirty-one out of the 55 asthma patients showed increased concentrations of total IgE in serum (>100 kU/L), and 21 of those had IgE antibodies to SAE mix. Consequently, 10 subjects had an increased total IgE, but no IgE antibodies to SAE mix. 12 sera had a total IgE above 500 kU/L, and 9 were positive, 3 negative for IgE-antibodies to SAE. These data suggest that in some patients, other superantigens than the once tested here may also play a role, e.g. *Streptococcus*. We therefore proposed a crucial role for SEs in the pathophysiology of upper and lower airway disease, linked to severity of eosinophilic inflammation, total IgE synthesis, but also clinical disease severity, to be confirmed in larger population as well as in confirmatory treatment studies.

We also studied the expression of total IgE and IgE-antibodies to SEs in chronic obstructive pulmonary disease (COPD) patients, smokers without COPD, and healthy controls [51]. SE-IgE antibodies were found in 1/10 controls and 1/16 smokers, but in 7/18 patients with stable disease (38.9%) and 21/54 patients with exacerbated COPD (38.9%). The IgE concentrations of patients with stable or exacerbated COPD were significantly higher than those of smokers or controls. Furthermore, IgE to SEs decreased significantly in the exacerbated patients during hospitalization, going along with a significant increase in FEV1. These data suggest a role for superantigens in exacerbated COPD similarly to that in severe asthma.

CLINICAL IMPLICATIONS AND PERSPECTIVES

In summary, there is accumulating evidence that superantigens, primarily derived from *S. aureus*, but possibly also from other sources such as Streptococcus, fungi (AFS) or viruses [52], may have a major impact on upper and lower airway disease such as nasal polyposis and asthma. Superantigens at least appear to modify, if not cause, severe airway disease [14,53]. *Staphylococcal* enterotoxins may furthermore affect treatment possibilities, as it was shown that these compounds may alter steroid sensitivity and expression of glucocorticoid receptor beta [54]. Dexamethasone caused a 99% inhibition of phytohemaglutinine (PHA)-induced PBMC proliferation, but only a 19% inhibition of the SEB-induced, 26% inhibition of the TSST-1, and 29% inhibition of the SEE-induced PBMC proliferation, demonstrating that superantigens can induce steroid insensitivity. At the same time, stimulation of normal PBMCs with SEB induced a significant increase of glucocorticoid receptor beta compared with PHA and unstimulated cells, a possible mechanism to induce glucocorticoid insensitivity.

For diagnostic purposes, *S. aureus* can be detected in the middle nasal meatus by swabs, but would only poorly predict production of and immune response to its enterotoxins. The potential production of enterotoxins by these germs, once cultured, can be shown by PCR or protein assays, but clinical studies to show the clinical relevance in an individual patient have not yet been

performed. The ability to produce enterotoxins by a given germ may also vary due to varying conditions in the nasal environment or number of colonies present. In contrast, the presence of IgE antibodies to SEs indicates a former or present stimulation of the local immune system by the respective enterotoxin, and can be tested in tissue homogenates. A polyclonal IgE response, high total IgE and increased eosinophilic mediators (ECP) would indicate the activity of the superantigens. Furthermore, *Staphylococcus* can now be stained intraepithelially by immuno- histochemistry, however, a positive staining would again not necessarily predict a specific immune response.

The potential therapeutic effect of a treatment to eradicate *S. aureus* in polyp disease or asthma has not been studied yet, but large-scale DBPCR studies are currently ongoing. From atopic dermatitis (AD), a disease sharing the modifying effects of *Staphylococcal* superantigens on inflammation and disease severity, we can deduce therapeutic approaches. The skin of up to 100% of patients with AD is colonized with *S. aureus*, of which up to 65% have been shown to produce enterotoxins with superantigenic properties. Ten patients were treated orally with antibiotics, chlorhexidine ointment was applied to the skin, and the anterior nares were treated with mupirocin ointment, and a bath containing potassium permanganate was taken daily [55]. In addition, their partners were treated topically. The Severity Scoring in AD (SCORAD) score decreased in nine of 10 patients who received antimicrobial treatment, and this effect was more pronounced in patients with a higher baseline SCORAD. Thus, antimicrobial treatment leads to a significant, albeit temporary improvement of AD in patients who were colonized with *S. aureus*. A similar effect may be anticipated for nasal polyps, however, needs to be confirmed. Other approaches, such as long-term antibiotic treatment with intracellular activity in combination with corticosteroids to decrease the immune response and increase steroid sensitivity, antibiotic treatment with intracellularly active drugs, or vaccination therapy against the germs might be developed in the future for sustained treatment success.

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