Role of staphylococcal superantigens in upper airway disease

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Purpose of review

Chronic rhinosinusitis with nasal polyps often represents a chronic severe inflammatory disease of the upper airways and may serve as a model for lower airway diseases such as late-onset intrinsic asthma. Enterotoxins derived from *Staphylococcus aureus* have been implicated in the pathophysiology of nasal polyps as disease-modifying factors; recent findings using therapeutic proof-of-concept approaches support this hypothesis.

Recent findings

Nasal polyps (chronic rhinosinusitis with nasal polyps) are characterized by a T-helper-2 dominated cytokine pattern that includes interleukin-5 and formation of immunoglobulin E. This is in contrast to chronic rhinosinusitis without polyps, which exhibits T-helper-1 biased cytokine release. It is now evident that the cytokine environment is decisive regarding the impact of *S. aureus* derived enterotoxins, which function as superantigens. *S. aureus* enterotoxin B further shifts the cytokine pattern in nasal polyps toward T-helper-2 cytokines (increases greater than twofold for interleukin-2, interleukin-4 and interleukin-5), but it disfavours the T-regulatory cytokines interleukin-10 and transforming growth factor-β_1. Furthermore, *S. aureus* derived enterotoxins influence local immunoglobulin synthesis and induce polyclonal immunoglobulin E production, which may contribute to severe inflammation via activation of mast cells.

Summary

From this new understanding of chronic rhinosinusitis with nasal polyps, new therapeutic approaches emerge such as anti-interleukin-5, anti-immunoglobulin E, and antibiotic treatment. These may enlarge the nonsurgical armentarium.

Keywords

immunoglobulin E, interleukin-5, nasal polyps, *Staphylococcus aureus*, superantigens

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Introduction

Staphylococcal enterotoxins, as well as molecules derived from *Streptococcus pyogenes* and some viruses, are able to activate T cells via the T cell receptor–major histocompatibility complex class II complex, independent from the antigen-specific groove, by binding to the variable β-chain of the T cell receptor [1]. The susceptibility of a T cell to those superantigens is therefore dependent on the usage of a specific β-chain repertoire, which leads to activation of abundant T cells in a given tissue. Once activated, T cells can orchestrate a severe inflammation, including polyclonal activation of B cells and recruitment of eosinophils (see for review [2•]). Nasal polyp disease appears to be an excellent model in which to study superantigen-driven persistent airway disease.

The link between *Staphylococcus aureus* and nasal polyp disease

The finding of immunoglobulin (Ig)E antibodies to *S. aureus* enterotoxins in nasal polyp tissue homogenates [3] indicated for the first time that these superantigens could be involved in the pathogenesis of nasal polyps. Nasal polyps, also referred to as chronic rhinosinusitis with nasal polyps (CRSwNP) [4], are characterized by an eosinophilic type of inflammation, driven by interleukin-5 and eotaxin, which together orchestrate the chemotaxis, activation and survival of eosinophils [5–7]. This cellular and cytokine pattern contrasts with chronic rhinosinusitis without nasal polyps (CRSsNP) – a disease in which interferon (IFN)-γ and transforming growth factor-β_1 are key players [8••]. We demonstrated that CRSwNP represents a T-helper-2 (Th2)-biased inflammation, whereas CRSsNP exhibits a Th1-cell pattern [8••]. The T-cell bias most probably contributes to the likelihood that *S. aureus* will colonize the mucosa, but it also creates an environment in which superantigens can or cannot exert their full activity.

We previously reported an increased colonization rate of *S. aureus* in nasal polyps, but not in CRSsNP [9]. Colonization with *S. aureus* was present in more than 60% of patients with polyps, with rates as high as 87% in the

subgroup with asthma and aspirin sensitivity, which were significantly higher than in control individuals and patients with CRSsNP (33% and 27%, respectively). IgE antibodies to *S. aureus* enterotoxins were present in 28% in polyp samples, with rates as high as 80% in the subgroup with asthma and aspirin sensitivity, as compared with 15% in control individuals and 6% in patients with CRSsNP, respectively [9]. The presence of specific IgE against *S. aureus* enterotoxins was also coincident with higher levels of interleukin (IL)-5, eotaxin and eosinophil cationic protein (ECP). Moreover, an increased number of T cells expressing the T cell receptor β-chain variable region known to be induced by microbial superantigens was detected in CRSwNP and correlated with the presence of specific IgE against *S. aureus* enterotoxin [10]. These findings confirm the role played by S. *aureus* enterotoxins as disease modifiers specifically in CRSwNP.

S. aureus enterotoxin B exposure in nasal polyps favours T-helper-2 cytokines and disfavours T-regulatory cytokines

In a recent study, we sought to elucidate the modulatory effects of *S. aureus* enterotoxin B (SEB) on nasal polyp tissue, which exhibits a Th2 bias, and to determine possible differences in response from unbiased nasal control tissue [11••]. Spontaneous release of cytokines was significantly greater in polyps than in inferior turbinates for IL-5, IL-13, tumour necrosis factor-α and IL-10, as was expected based on the findings of previous studies, without differences between allergic and nonallergic patients. Twenty-four hours of SEB stimulation caused significant increases in Th1 and Th2 cytokines (IFN-γ, IL-2, IL-4, IL-5, IL-10 and IL-13) in inferior turbinates and polyps compared with culture medium exposure. This release was significantly greater in polyps than in inferior turbinates for all of these cytokines, although the number of $CD3^+$ T lymphocytes was equivalent between inferior turbinates and polyps. When the relative increase in cytokine release with SEB stimulation was calculated, it became apparent that SEB shifts the cytokine pattern in nasal polyps toward the Th2 cytokines (increase greater than two-fold for IL-2, IL-4 and IL-5), but that it disfavours the T-regulatory cytokines IL-10 (by a factor of 0.58) and transforming growth factor-β_1 (by a factor of 0.73).

This study clearly demonstrated that SEB can polarize mucosal inflammation to a Th2 pattern, and furthermore that it may contribute to persistent inflammation by suppression of induced T-regulatory lymphocytes [11••]. These findings also corroborate others demonstrating that superantigens inhibit naturally occurring $CD4^+CD25^+$ regulatory T-cell activity [12•] on T effector cell proliferation by an antigen-presenting cell dependent contact mechanism, and induction of glucocorticoid-induced tumour necrosis factor (TNF) receptor-related protein ligand (GITR-L) on monocytes. Of interest, such polarization was observed in Th2-biased mucosal tissue but not in unbiased control tissue, emphasizing the importance of the cytokine environment in a given tissue in determining the impact that superantigens have on T effector and regulatory cells.

Superantigens modulate local immunoglobulin production in nasal polyps

Consistent with the increase in IL-5 and other Th2 cytokines, a significant increase in local IgE antibodies can be observed in polyp patients, independent of allergy skin test results or serum IgE measurements. Furthermore, there is a strikingly high correlation between IL-5 and IgE antibody concentrations in nasal polyp homogenates, supporting the hypothesis that *S. aureus* enterotoxins, apart from T cells, also modify B and plasma cells [7]. In fact, there is accumulating evidence that *S. aureus* enterotoxins 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 [13]. Studies with toxic shock syndrome toxin (TSST)-1 indicated that staphylococcal superantigens may play an important role in the modulation of allergic disease, because they may augment isotype switching and synthesis of IgE, both *in vitro* [14] and *in vivo*, in a severe combined immunodeficient mouse model [15]. 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 [14] provided evidence for a direct effect by demonstrating TSST-1-induced expression on B cells of B7.2, 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 hybridization [16–18], supporting the hypothesis of truly local IgE synthesis in the airway mucosa. It is highly likely (but remains to be proven) that this is also the case for CRSwNP.

We recently described a markedly increased number of plasma cells in sinonasal mucosal tissue samples from CRSwNP patients as compared with those from CRSsNP patients and control individuals [8••]. We have since extended these findings with *S. aureus* specific data. In the follow-up study, high concentrations of IgE, IgA and IgG were measured in nasal polyp homogenates, and these concentrations were significantly greater in CRSwNP than in CRSsNP patients and control individuals, but this was not the case in serum [19•]. Furthermore, levels of IgG subclasses (IgG_1, IgG_2, IgG_3 and

IgG_4) were measured and expressed in absolute concentrations and percentages of the sum of the IgG subclasses. In accordance with the higher levels of total IgG in nasal polyp homogenates, we found significantly higher concentrations of all IgG subclasses in nasal polyp homogenates than in CRSsNP and control samples. IgG_1 and IgG_2 represented the greatest fractions, whereas IgG_3 was the smallest in all groups both in serum and homogenates.

Of interest, nasal polyp homogenates in which *S. aureus* enterotoxin–IgE antibodies were detectable had significantly greater concentrations of IgG, IgG_4 and IgE than did those without *S. aureus* enterotoxin specific IgE [19•]. Furthermore, we observed a significantly greater fraction of IgG_4 in polyp homogenates that were positive for IgE antibodies to *S. aureus* enterotoxins, positively correlating with IgE and the number of plasma cells, whereas the IgG_2 fraction was significantly lower. These changes were not reflected in the serum of patients; the presence of *S. aureus* enterotoxin–IgE antibodies in tissue or serum did not influence immunoglobulin concentrations in serum, confirming the notion of a local impact of superantigens – via direct action on B cells or indirectly via T-cell derived cytokines – on immunoglobulin synthesis.

The functional role played by local IgE antibodies in polyp disease must be investigated and is called into question by observations in ragweed-sensitive polyp patients, who do not exhibit specific seasonal changes in symptoms or mediators [20]. In laboratory experiments in which basophils armed with specific IgE to enterotoxin B were exposed to the superantigen, however, the basophils degranulated rapidly [21]. Thus, enterotoxin-specific IgE antibodies could potentially contribute to the disease via degranulation of mast cells in polyp tissue, as well as other IgE antibodies with specificities against inhalant allergens. Indeed, because of the polyclonality, hundreds of allergens could possibly induce a constant degranulation of those mast cells, a condition that has actually been observed in polyp tissue. Based on these observations, anti-IgE treatment could be expected to suppress the IgE-mediated inflammatory cascade in a nonallergic disease such as nasal polyps, similar to its activity in allergic respiratory disorders. A proof-of-concept study is currently underway at the Ear, Nose and Throat Department of the Ghent University Hospital.

The impact of superantigens on eicosanoids

When comparing eicosanoid production in patients with chronic rhinosinusitis between those who have and those who do not have nasal polyps, concentrations of the leukotriene C_4 synthase, 5-lipoxygenase and cysteinyl leukotrienes increased in parallel with the severity of eosinophilic inflammation [22]. Other metabolites such as cyclo-oxygenase-2 and prostaglandin E_2 significantly decreased with disease severity; IL-5 and ECP correlated directly with cysteinyl leukotrienes and inversely with prostaglandin E_2 concentrations. Thus, nasal polyps typically exhibit an upregulation of proinflammatory cysteinyl leukotrienes and a downregulation of prostaglandin E_2, which is considered an anti-inflammatory metabolite and also may influence the formation of T-regulatory cells [23].

We extended our observations by demonstrating that the production of cysteinyl leukotrienes, leukotriene B_4 and lipoxin A_4 is upregulated in polyp tissue from patients exhibiting an immune response to *S. aureus* enterotoxins as compared with tissue from nasal polyp patients who were negative for *S. aureus* enterotoxin–IgE [24•]. Again, the levels of the eicosanoids correlated with markers of eosinophil activation and survival (ECP and IL-5) and with concentrations of IgE antibodies and *S. aureus* enterotoxin specific IgE. A direct mechanism by which enterotoxins can modify prostanoid metabolism and related functions has not yet been identified, however. We recently isolated fibroblasts (relevant structural cells that contribute to eicosanoid production) from inferior turbinate tissue and cultured the cells in the presence of different concentrations of SEB [25]. Pre-incubation with IFN-γ was performed to induce expression of major histocompatibility complex II receptors. After pre-incubation with but not without IFN-γ, SEB significantly downregulated prostaglandin E_2, cyclo-oxygenase-2 and E-prostanoid receptor 2 mRNA expression. These findings point to the direct role played by bacterial superantigens in regulating eicosanoids, and thus inflammatory processes in upper airway tissues, via prostaglandin E_2 and EP_2 downregulation.

Implications for treatment of nasal polyps

To summarize, *S. aureus* frequently colonizes the nasal and ostiomeatal mucosa in polyp disease, and releases superantigens, which interfere with the local T and B cells. There is accumulating evidence that superantigens may also have a major impact on lower airway disease such as asthma, chronic obstructive pulmonary disease and early wheezing [26••]. *S. aureus* enterotoxins induce an amplification of the synthesis of the Th2 cytokine IL-5, which increases eosinophil survival; local polyclonal formation of IgE antibodies, which possibly stimulate continuous mast cell degranulation; and, finally, suppression of natural and induced T-regulatory cells, which could be crucial for the persistent nature of the severe eosinophilic inflammation. Nevertheless, the therapeutic armentarium for CRSwNP is limited to topical or systemic glucocorticosteroids, which decrease Th2 cytokine release and thus partially suppress eosinophilic inflammation. Staphylococcal enterotoxins may impair such treatment possibilities, however, because it was demonstrated that

superantigens may alter steroid sensitivity and expression of glucocorticoid receptor β [27]. Innovative therapeutic approaches are clearly needed, especially in severe nasal polyp disease with asthma co-morbidity and recurrent disease.

For atopic dermatitis, a disease that shares the modifying effects of staphylococcal superantigens on inflammation and disease severity, the benefit of antibiotic eradication combined with local disinfection is established [28]. The potential therapeutic benefit of an antibiotic treatment in polyp disease – for proof of principle – has recently been studied. A 3-week treatment regimen significantly decreased polyp size versus placebo for 8 weeks, in accordance with significant suppression of inflammatory parameters (van Zele T, Gevaert P, Bachert C, unpublished data). Further studies will be required to demonstrate the efficacy and tolerability of long-term antibiotic intervention, of vaccination against *S. aureus*, and of enterotoxin antagonists [29•].

The possibility of an anti-IgE treatment with monoclonal humanized antibodies (discussed above), based on the hypothesis that the local polyclonal *S. aureus* enterotoxin induced production of IgE-antibodies in polyps contributes to the inflammation via continuous mast cell degranulation, once again requires a proof-of-principle study. Another approach to interfere with superantigen-induced downstream events would consist of an anti-IL-5 treatment. In a double-blind, placebo-controlled, randomized safety and pharmacokinetic study [30••], 24 patients with bilateral polyps were randomly assigned to receive a single intravenous infusion of a humanized antihuman IL-5 monoclonal antibody, at 3 mg/kg or 1 mg/kg, or placebo. We evaluated safety and pharmacokinetics of the monoclonal antibody, whereas biological activity was assessed by nasal peak inspiratory flow, symptoms, endoscopic evaluation of polyp size, peripheral eosinophil counts, peripheral and local IL-5, soluble IL-5 receptor and ECP levels. We demonstrated that a single injection of anti-human IL-5 is safe and well tolerated, and blood eosinophil numbers and concentrations of ECP and soluble IL-5 receptor α were reduced after treatment in serum and nasal secretions. Individual nasal polyp scores improved in only half of the treated polyp patients, however, and responders could be differentiated from nonresponders by increased IL-5 concentrations in nasal secretions at baseline; nasal IL-5 levels above 40 pg/ml were found to predict the response to anti-IL-5 treatment [30••]. A recent study with repeated anti-IL-5 injections of an antibody with greater affinity, using nasal endoscopy and computed tomography scans before and after treatment, yielded very promising results, again in a subpopulation of patients (Gevaert P, Bachert C, unpublished data). It appears that measurement of biomarkers such as *S. aureus* enterotoxin specific IgE antibodies, total IgE, or IL-5 could be useful for the making optimal treatment choice in nasal polyps, a disease that is amplified markedly by *S. aureus* enterotoxins.

Conclusion

There is increasing evidence that *S. aureus* derived enterotoxins amplifies the eosinophilic inflammation in CRSwNP in different ways; amplification of the release of Th2 cytokines and IgE formation, and downregulation of T-regulatory cytokines may all contribute to the severe and chronic inflammatory process. This opens the field for new therapeutic approaches, extending current anti-inflammatory treatments such as local or oral glucocorticosteroids with anti-IL-5, anti-IgE and antibiotic treatments. A challenge for the future will be to develop predictors of response to those treatments, which have demonstrated efficacy in a substantial subgroup of patients with CRSwNP.

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