REVIEW ARTICLE

Role of imbalance of eicosanoid pathways and staphylococcal superantigens in chronic rhinosinusitis

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Abstract

Chronic rhinosinusitis (CRS) is a multifactorial disease of the upper airways with a high prevalence (approximately 11%) in the general population. Different immune and inflammatory mechanisms are involved in its pathogenesis. Alterations in the arachidonic acid pathway (leading to an imbalanced production of eicosanoids) have been linked to the pathophysiology of different diseases especially nasal polyposis, asthma, and aspirin-exacerbated respiratory disease. Furthermore, viral and bacterial infections have been identified as important factors amplifying the pro-inflammatory reactions in these pathologies. This review summarizes the impact of an imbalance in the eicosanoid pathway and the effect of *Staphylococcus aureus* enterotoxins on the regulation of the pro-inflammatory network in CRS and their translation into disease severity.

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Chronic rhinosinusitis (CRS) is a multifactorial inflammatory disease of the nasal and paranasal sinuses with a high impact on the quality of life (1, 2). CRS may or may

not be accompanied by polyp formation and often occur in combination with other airway pathologies like asthma, allergy, aspirin intolerance, and cystic fibrosis (3). Although a considerable amount of research has been dedicated to the study of its pathogenesis, the inflammatory mechanisms underlying the disease remain unclear.

Bacterial superantigens (SAGs) are recently discovered players in the regulation of the inflammatory process in airway inflammatory diseases (4–6). *Staphylococcus aureus* (*S. aureus*), a pathogenic Gram-positive bacteria, often colonize the human skin, the upper respiratory tract, and the intestinal tract. This microorganism has the capability of producing and releasing enterotoxins with superantigenic activity. These so-called staphylococcal SAGs have strong immune-modulatory and pro-inflammatory effects able to modify the functions of T and B cells, eosinophils, inflammatory and structural cells. *Staphylococcal* enterotoxins (SEs) have been shown to influence type 2 T-helper cell-polariza-

Abbreviations

15-(S)-HETE 15-Hydroxyeicosatetraenoic acid; 5-(S)-HETE 5-Hydroxyeicosatetraenoic acid; ALOX15 15-Lipoxygenase; ALOX5 5-Lipoxygenase; AA arachidonic acid; COX-1 cyclooxygenase-1; COX-2 cyclooxygenase-2; CRTH2 chemoattractant receptor-homologous molecule expressed on T_H2 cells; CRSsNP chronic rhinosinusitis without nasal polyps; CRSwNP chronic rhinosinusitis with nasal polyps; CysLTs cysteinyl leukotrienes; CysLT1 cysteinyl leukotriene receptor 1; CysLT2 Cysteinyl leukotriene receptor 2; ECP eosinophil cationic protein; LTB₄ leukotriene B₄; LTC₄S leukotriene C₄ synthase; LTRs leukotriene receptors; LXA₄ lipoxin A₄; LXs lipoxins; LTs leukotrienes; NSAIDs nonsteroidal anti-inflammatory drugs; SAGs superantigens; SEs *Staphylococcus aureus* enterotoxins; SEB *S. aureus* enterotoxin B.

tion, eosinophilic inflammation, and polyclonal IgE production and hence to contribute to the amplification and maintenance (chronicity) of the inflammatory mechanisms operating in airway diseases (4).

In the last two decades, it has been demonstrated that alterations in eicosanoid synthesis play an important role in airway inflammatory conditions like rhinosinusitis, nasal polyposis, allergic rhinitis, and asthma. This imbalance is characterized by increased synthesis of cysteinyl leukotrienes (CysLTs) by inflamed tissue in contrast to slightly increased prostaglandin E_2 (PGE_2) release when compared with normal tissue, which correlates with the inflammatory pattern and severity of the diseases. In this review, we discuss the impact of imbalance in the eicosanoid pathway and the effect of *S. aureus* enterotoxins in the regulation of the pro-inflammatory network in CRS, and how they contribute to the severity of the disease.

Eicosanoid biosynthetic pathway

Eicosanoids are inflammatory mediators that regulate crucial homeostatic functions such as inflammation, immunity, and messenger networks in the central nervous system (7). Their synthesis starts when the cell activated by mechanical trauma, cytokines, pathogens, or other stimuli triggers the release of membrane-bound fatty acids that are then metabolized via

the cyclooxygenase (COX) and/or the lipoxygenase pathways (7) (Fig. 1).

The COX pathway involves the COX-1 and COX-2 enzymes that convert the arachidonic acid (AA) to prostacyclins (PGI_2), prostaglandins (PGD_2 , PGE_2 , $PGF_{2\alpha}$), and thromboxanes (TXA_2 , TXB_2) (8). COX-1 is mainly expressed constitutively, and COX-1-dependent prostaglandins are thought to control a number of physiological 'homeostatic' functions (8). The expression of COX-2, in contrast, seems to be inducible in response to pro-inflammatory stimuli, and COX-2-dependent prostaglandins may have both pro- and anti-inflammatory actions (8).

The lipoxygenase pathway involves the enzymes ALOX5 leading to the production of leukotrienes (LTs) and the ALOX15/12 for the synthesis of lipoxins (LXs). The LTs group comprises leukotriene B_4 (LTB_4) and CysLTs LTC_4 , LTD_4 , and LTE_4 (9). LTB_4 is a potent neutrophil chemoattractant and regulates mainly leukocyte activation, migration, and apoptosis by binding to the BLT_1 and BLT_2 receptors (9). CysLTs have a potent bronchoconstriction activity and act by binding to the cysteinyl leukotriene receptor 1 ($CysLT_1$) and $CysLT_2$ receptors (10).

Lipoxins (LXA_4 and LXB_4) have been identified as endogenous 'braking signals' with potent anti-inflammatory and pro-resolving actions (11). Their synthesis occurs via three transcellular routes: the first involves the generation of LTA_4

Figure 1 Arachidonic acid cascade leading to the formation of cysteinyl leukotrienes, prostaglandins, thromboxanes, lipoxins, and aspirin-triggered lipoxins.

by ALOX5, present in cells of myeloid lineage, which is taken up by platelets where it is metabolized to form LXA₄ by the enzyme ALOX12 (12). A second route involves the generation of 15-Hydroxyeicosatetraenoic acid (15(S)-HETE) by epithelial- and/or monocyte-derived ALOX15 that serves as a substrate for ALOX5 in neutrophils to produce LXA₄ and LXB₄ (12). The third and additional route is the so-called aspirin-triggered 15-epi-LX (ATLXs) pathway. In this pathway, intake of aspirin irreversibly inhibits COX-1 and acetylates COX-2 enzyme resulting in the formation of 15(S)-HETE, which is then transformed by leukocyte-derived ALOX5 to 15-epi-LXA₄ or 15-epi-LXB₄ (13). Both LXA₄ and 15-epi-LXA₄ bind and activate lipoxin receptors mostly leading to the resolution of inflammation (13).

Implications of eicosanoid imbalance on chronic sinus diseases

The imbalance of the eicosanoid pathway in paranasal sinus diseases and especially nasal polyps has been demonstrated by several studies.

Leukotrienes

Cysteinyl leukotrienes are potent inducers of airway inflammation by promoting inflammatory cell (mainly eosinophils) recruitment and activation (14). They also influence airway remodeling by inducing smooth muscle cell and epithelial cell proliferation (15). In inflamed nasal mucosa, LTs promote nasal congestion and edema by inducing vascular leakage and vasodilatation (16). Concentrations of ALOX5, leukotriene synthase (LTC₄S), and CysLT₁ receptor are significantly increased in nasal polyp tissue from chronic rhinosinusitis with nasal polyp patients (CRSwNP) compared to chronic rhinosinusitis without polyps (CRSsNP) and control subjects (17). CysLTs levels in patients with CRSwNP positively correlate with the number of activated eosinophils as well as with eosinophil cationic protein (ECP), IL-5, and IL-5R α concentrations (17). Activated eosinophils infiltrating the nasal polyp tissue are the probable major biosynthetic source of CysLTs and CysLT₁ receptor (18, 19). Although the physiological mechanisms regulating the biosynthesis of CysLTs by these cells are not clear yet, it is known that 'activated' eosinophils produce high quantities of LTC₄ after priming with factors such as eotaxin, platelet-activating factor (PAF), and IL-5 (14). Consequently, the up-regulation of LTs acts as a paracrine and autocrine mechanism for chemotaxis and survival of eosinophils, a mechanism likely to operate in CRSwNP.

Controversial results regarding the regulation of LTB₄ and its receptors (BLT₁ and BLT₂) have been reported. In a study in 2006, we did not find any differences in the protein levels of LTB₄ and mRNA for BLT₁ and BLT₂ between CRSsNP, CRSwNP groups, and normal nasal mucosa groups (18). Another study, however, reported that levels of LTB₄ are increased in CRSwNP patients with allergy in comparison with nonallergic and control subjects (16). The reason for this discrepancy may be due to differences in the

study groups or in the complexity of the LTB₄ pathway. It could be that synthesis of LTB₄ in CRS and especially in CRSwNP greatly depends on the balance between the different inflammatory cells present in the tissue and the concentration of the enzymes involved in its synthesis in each of these cell types.

Prostaglandins

Roca-Ferrer et al. (20) reported for the first time that nasal polyp tissue has a diminished capacity to produce PGE₂ and up-regulate COX-1, COX-2, and prostaglandin E receptor EP2 under pro-inflammatory conditions. Further, in an attempt to find a link between PG pathway and eosinophilic inflammation observed in CRSwNP, we observed that mRNA expression of prostaglandin E receptors EP1 and EP3 is down-regulated in CRSwNP tissue in contrast to EP2 and EP4 receptors that are significantly increased in both CRS groups when compared with control tissue (21). Of interest, levels of EP2 and EP4 receptors did not correlate with eosinophil numbers or eosinophil activation markers, in contrast to PGE₂ which was down-regulated and inversely correlated with eosinophilic inflammation in CRSwNP patients. Expression of EP2 and EP4 receptors in eosinophils from asthmatic patients was previously reported by Mita et al. (22). However, in that study, EP4 was suggested as the only functional receptor in these cells and its signaling might be dependent on the level of exposure to PGE₂ (22). The impact of PGE₂ and its receptors on eosinophil function in CRS is still unclear. PGE₂ attenuated the synthesis of LTC₄ by eosinophils isolated from normal and atopic individuals (23). However, Peacock et al., (24) showed that PGE₂ inhibited eosinophil apoptosis, prolonging their survival and activation. These data suggest that effect of PGE₂ in CRS may depend on the regulation of its receptors, inflammatory milieu, and more importantly the contribution of other cells as explained below.

Fibroblasts are an important source of PGs in the airways; however, controversial data in CRSwNP have been reported. Liu et al. (25) found that nasal polyp fibroblasts (NPFs) are able to produce significantly higher amounts of constitutive COX-2 mRNAs compared to fibroblasts from nasal inferior turbinate; Roca-Ferrer et al., (20) however, showed that NPFs have significantly lower levels of COX-1 and COX-2 mRNA and were unable to induce their expression after IL-1 β stimulation. Of interest, both findings can be extrapolated to the inflammatory pattern observed in nasal polyposis. It has been suggested that up-regulation of COX-2 expression by fibroblasts may contribute to nasal polyp development by promoting vascular dilatation (25). Furthermore, PGE₂ may also influence tissue remodeling by inducing mucin secretion, a main feature of CRSwNP (26). However, an important aspect to consider is that COX-2 may stimulate tissue remodeling by increasing TGF- β and collagen synthesis, but these two molecules are down-regulated in nasal polyp tissue (27). Analyzing altogether, one might reasonably question the role of PGE₂ in the pathogenesis of nasal polyposis. It does not seem possible to give an answer at this stage but it appears that regulation of this pathway greatly

depends on the individual contribution of the different cell types and the cytokine milieu that surround them.

Finally, PGD₂, one of the major mast cell-derived prostanoids, being released during the early phase of allergic reactions, is highly secreted after IgE stimulation of nasal polyp tissue (28). Okano et al. (29) showed that hematopoietic prostaglandin D synthase (hPGDS) and microsomal prostaglandin E synthase-1 (m-PGES-1) display an opposite regulation in CRSwNP. In that study, transcript levels of hPGDS were increased in CRSwNP compared to CRSsNP and healthy subjects and positively correlated with the clinical disease severity and with the number of activated eosinophils (29). However, m-PGES-1 was down-regulated in CRSwNP and inversely correlated with the severity of sinusitis (29). On the other hand, distribution and expression of PGD₂ receptors also seem to be counter-regulated. DP1 receptor expression is increased in tissue-infiltrating inflammatory and constitutive cells in CRSwNP compared to noninflamed nasal mucosa (30). CRTH₂ in contrast was mainly localized in inflammatory cells (eosinophils and T cells) and showed two distinct expression patterns. One pattern showed increased expression of the receptor in CRSsNP, and a second pattern demonstrated low levels in the more severe cases (CRSwNP) and an inverse correlation with IL-5 and eotaxin levels (30). Further, in the same study, incubation of nasal polyp tissue explants with PGD₂ significantly reduced CRTH₂ mRNA, suggesting that different to DP₁, transcriptional regulation of this receptor may be linked to a negative feedback mechanism orchestrated by PGD₂ and probably eosinophil-associated mediators (30). We later demonstrated that PGD₂ released after 30-min stimulation of nasal polyp tissue explants with IgE promotes the migration of T_H2 cells through a CRTH₂-dependent mechanism (31). However, IgE increased the transcript levels of both DP₁ and CRTH₂ receptors in the tissue. These discrepancies regarding CRTH₂ response between the studies may be due to differences in the target cell type and/or experimental conditions. In addition, it could be that during the early phase of the allergic reaction, up-regulation of DP1 and CRTH₂ receptors is needed in order to recruit inflammatory cells to the tissue. Once the late phase is started, where cytokines and other mediators are synthesized, a decrease in the expression of the receptor will be needed to control the local inflammatory reaction, as suggested by Yamamoto (30).

Lipoxins

Several studies have demonstrated that the progression of inflammation in several airway chronic diseases is associated with deficiencies in lipoxin production and/or an imbalance between pro-inflammatory eicosanoids and lipoxins (32). However, knowledge on their expression and role in upper airway diseases is limited. ALOX15 mRNA and LXA₄ levels are up-regulated in CRSwNP patients compared to control subjects (17). In addition, ALOX15 was localized in the epithelium and subepithelium of CRS and even more in nasal polyp tissues (data not published), confirming its expression in the nasal mucosa. This positive immunostaining correlated

with the amount of activated eosinophils infiltrating the nasal polyp epithelium and mucosa, suggesting that the increased levels of LXA₄ may be related to a transcellular interaction between eosinophils and tissue-resident cells, such as cytokine-primed endothelial or epithelial cells. LXA₄ may influence cellular electrochemical properties by inducing chloride (Cl⁻) secretion and cellular calcium (Ca²⁺) mobilization (33). Intracellular Ca²⁺ plays a central role in epithelial cellular function such as ion or protein secretion and cell tonicity. Although not proven yet, this imbalance of sodium (Na⁺)/Cl⁻ levels that alter epithelial permeability may lead to the accumulation of extracellular fluid promoting edema formation, a hallmark of nasal polyposis. In summary, this points out that not the absolute amount of LXs but the balance with other pro-inflammatory molecules such as LTs may be of great importance, and that these molecules may play a crucial role via modifying cellular electrochemical and physicochemical properties.

Eicosanoid imbalance in aspirin-exacerbated respiratory disease

Aspirin-exacerbated respiratory disease (AERD) is a distinct clinical syndrome of intractable inflammation of both upper and lower respiratory tracts, which is characterized by chronic eosinophilic rhinosinusitis with asthma, nasal polyposis and hypersensitivity to aspirin and other nonsteroidal anti-inflammatory drugs that inhibit COX-1 (34–36). The hallmark of the disease is the precipitation of violent asthmatic attacks (accompanied usually by nasal blockage and ocular symptoms) by aspirin and other COX-1 inhibitors (35). The prevalence of this syndrome in the general population is of about 0.6–2.5%; however, it occurs in 4.3–21% of patients with bronchial asthma and even more (15–40%) in subjects with asthma and nasal polyposis (35). AERD represents probably the most severe form of chronic sinusitis: 80–99% of patients have radiological changes in sinuses and up to 60% suffer from nasal polyposis (35).

At the biochemical level, this syndrome is characterized by profound alterations in eicosanoid biosynthesis, which constitutes the basis of the COX theory of AERD (37). The balance between pro-inflammatory acting CysLTs and PGs (namely PGD₂), anti-inflammatory PGs (namely PGE₂), and lipoxins is deregulated in AERD patients (38–40). Increased production of CysLTs in these subjects is present at baseline and is increased further following aspirin challenge, measurable in urine, nasal, bronchial lavages, and breath condensates (39, 41). Furthermore, severity of reactions to aspirin is linked to higher levels of urinary LTE₄ and 9α11β-PGF₂ (a metabolite of PGD₂) expression following aspirin challenge (38). Nevertheless, the nasal mucosa and tissue of nasal polyps may largely contribute to overall production of eicosanoids. In 1993, Kowalski et al. (42) reported an increase in LT concentrations in nasal lavages from AERD subjects following nasal aspirin challenge, suggesting the link between the release of these metabolites and the clinical symptoms observed in these patients. In 1998, Andrzej Szczeklik from the University of Cracow, Stephen T. Holgate from Univer-

sity of Southampton, and Frank Austen from Harvard Medical School discovered a marked overexpression of baseline CysLTs in bronchoalveolar lavage (BAL) fluid of AERD patients, which in turn correlated with the number of LTC₄ synthase-positive cells in the bronchial mucosa and bronchial responsiveness to lysine-aspirin challenge (43). Later, we confirmed that the levels of CysLTs and the expression of ALOX5, LTC₄S, and CysLT₁ receptor are significantly up-regulated in the nasal polyp tissue of AERD patients and correlated with IL-5 and ECP concentrations (17, 19).

The regulation of PG synthesis in the disease is more complex. Levels of PGD₂ metabolites are increased at baseline and following aspirin challenge in AERD (38). On the other hand, AERD patients respond with a diminished capacity to produce anti-inflammatory acting PGE₂ in both upper and lower airways after bronchial aspirin challenge (44). Taking this one step further, Picado et al. (45) showed that COX-2 mRNA levels and NF- κ B activity are markedly lower in nasal polyp tissue from AERD subjects. These findings were corroborated by Kowalski et al. (46) who also demonstrated that nasal polyp epithelial cells isolated from AERD patients have a lower capacity to produce PGE₂ than those from non-AERD patients. Later, we demonstrated that COX-2 mRNA and PGE₂ concentrations are indeed significantly decreased in nasal polyp tissue from AERD patients and inversely correlated with the degree of eosinophilic inflammation (17). In the bronchial compartment, however, the situation is different. The group of Corrigan et al. (47) found that although concentrations of PGE₂ in BAL were similar in AERD and non-AERD patients, bronchial mucosa of AERD subjects had reduced percentages of T cells, macrophages, mast cells, and neutrophils expressing the EP2 receptor. Previously, Pierzchalska et al. (48, 49) showed that human bronchial fibroblasts and epithelial cells from AERD patients have low capacity to produce PGE₂, and this was linked to down-regulation of COX-1 protein. Surprisingly, Sanak et al. (50) observed that oral aspirin challenge decreased the systemic levels of two major PGE₂ metabolites only in the non-AERD group supporting the implication of a COX-1-dependent or an alternative COX-2-PGE₂ mechanism in the pathogenesis of this disease, which is in line with the fact that selective COX-2 inhibitor drugs are better tolerated than those blocking COX-1 enzyme.

Finally, contributions of ALOX15 metabolites such as lipoxins and 15(S)-HETE(s) in the pathogenesis of AERD cannot be excluded. In 2000, Sanak et al. (51) demonstrated for the first time that whole blood cells from asthmatic patients have the capacity to generate both LXA₄ and 15-ATLXs, but that AERD patients display a lower biosynthetic capacity than non-AERD subjects. This was later clinically confirmed by Yamaguchi et al. (40) who demonstrated decreased concentrations of both urinary 15-epi-LXA₄ and LXA₄ in patients with AERD. In upper airways, nasal polyp tissue from CRSwNP had higher concentrations of LXA₄ when compared to healthy nasal mucosa but those levels were decreased in patients with AERD (17). Results of the study conducted in 2009 by Kuna et al. support this finding.

They demonstrated that nasal challenge with lysine-aspirin induced the release of LTC₄ but showed a decrease in LXA₄ levels in AERD patients in contrast to non-AERD subjects who responded with no change in LTC₄ levels and an increase in LXA₄ (52). Moreover, alterations in the synthesis of 15(S)-HETE have been also demonstrated in AERD patients. This molecule is an intermediate metabolite of the LXs pathway and is a potent chemoattractant for eosinophils and neutrophils in the airways. Baseline levels of 15(S)-HETE are increased in exhaled breath condensates from AERD when compared to non-AERD subjects (53). Following, *in vitro* stimulation of peripheral blood leukocytes with aspirin, there is a generation of 15(S)-HETE only in AERD subjects and this mechanism may be modulated by EP1 and EP3 receptors and related to the expression of alternatively spliced variants of COX-1 enzyme (54, 55). The mechanisms regulating the synthesis of this metabolite in airways are not known. However, we can speculate that some factors probably cell specific operating only in AERD patients determine the release of free 15(S)-HETE instead of its usage in the synthesis of ATLXs.

Taking altogether we can state that the balance between pro- and anti-inflammatory eicosanoids is broken and plays a crucial role in the development and chronicity of CRS as shown in Fig. 2.

Staphylococcal SAgS

Superantigens are toxins of microbial or viral origin that cross-link antigen-presenting cells (APCs) and T cells by binding simultaneously to the major histocompatibility complex class II (MHC-II) and the T-cell receptors (TCRs) (56). They have an extreme ability to induce polyclonal activation of CD4⁺ and CD8⁺ T cells and, in contrast to conventional antigens, when presented on MHC-II, they are not processed and presented as short peptides (56). The hallmark for T-cell stimulation by SAgS is the specificity for the V β part of the T-cell receptor (TCR-V β) (56). SAgS possess a specific TCR-V β profile that allows the expansion and activation of those T cells bearing certain TCR-V β s, while others will be excluded (56). In addition, the TCR-V α subunit may interact with the β -chain of MHC-II and the TCR- α chain and influence in this way the T-cell activation by the SAgS (56). *Staphylococcus aureus* bacteria may secrete more than 10 different classical or egc-locus related enterotoxins (SEs), and their production is tightly dependent of the bacterial strain and host environment (57).

Staphylococcal SAgS and chronic sinus diseases

In the last decade, new evidences have raised supporting the role of staphylococcal-derived enterotoxins in the pathogenesis of chronic sinus diseases (58–61). For the first time, Bachert et al. (4) demonstrated the presence of specific IgE to *S. aureus* enterotoxins in nasal polyp tissue, which correlated with the severity of eosinophilic inflammation and the presence of asthma. Later, the same group demonstrated an increase in polyclonal IgE and the formation of a secondary

Figure 2 Balance of eicosanoid biosynthesis in chronic rhinosinusitis (CRS) compared to healthy nasal mucosa. CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; CRSwNP-AERD, chronic rhinosinusitis with nasal

polyps and aspirin-exacerbated respiratory disease. The magnitude of the changes are represented by the shape of the arrows: dashed arrows (less pronounced), solid arrows (most pronounced). AERD, aspirin-exacerbated respiratory disease.

lymphoid tissue in nasal polyps from CRSwNP patients associated with the presence of specific IgE-SEs and eosinophilic inflammation (62), suggesting the occurrence of a polyclonal B-cell activation because of the chronic microbial colonization and release of enterotoxins (62). Additionally, high total serum IgE and IgE-SEs levels have been observed in patients with allergic rhinitis, which also manifested sensitization to SEs (63).

Based on the previous studies, Corriveau et al. (64) demonstrated an intramucosal colonization of the *S. aureus* bacteria and detected that this was higher among CRSwNP patients vs healthy subjects and CRSsNP. However, the amount of bacteria found in the tissue did not correlate with the amplification of the T_H2-related inflammation found in the CRSwNP patients, suggesting that the formation of specific IgE-SEs rather than the bacterial colonization may be the crucial factor amplifying the inflammatory pattern in these patients. *Ex vivo* studies have confirmed that SEs mediate mast cell degranulation by binding to the IgE high-affinity receptor (FcεR1β) (60, 65). Short incubation (30 min) of nasal polyp tissue with staphylococcal surface protein A induced mast cell degranulation characterized by the production of histamine, CysLTs, and PGD₂ (65). On the other hand, long stimulation (24 h) with staphylococcal enterotoxin B (SEB) resulted in a significant increase in cytokines with a T_H2-skewed pattern in nasal polyp tissue (65). Huvenne et al. (66) showed that stimulation of human nasal epithelial cells with SEB induced the up-regulation of pro-inflammatory mediators

resulting in an increase in neutrophil chemotaxis and prolonged survival of eosinophilic granulocytes. These findings contribute to the understanding of SEs modulation of airway diseases.

Staphylococcal Sags and AERD

Within the CRSwNP group, AERD patients have a 87.5% colonization rate of *S. aureus* in the nasal mucosa (67). It was also confirmed that nasal polyp tissue of patients with AERD contains increased concentrations of total IgE and IgE-SEs when compared to their non-AERD counterparts and inferior turbinate tissue from healthy subjects (68). In that study, 54% of patients within the AERD group and 26% from the non-AERD showed detectable levels of IgE-SEs irrespective of the allergy status. However, a direct correlation between eosinophilic activation markers and IgE-SEs was only observed between patients with and those without SE immune responses in the non-AERD group. Further, Lee et al. (69) confirmed that the prevalence of specific IgE to SEB and TSST-1 is significantly higher in asthmatic patients compared to healthy controls, although no significant differences could be found between AERD and non-AERD subjects. Airway hyper-responsiveness was also significantly increased in asthma patients with detectable specific IgE-SEs compared to asthma patients without (69). In a recent study, we could demonstrate that stimulation of peripheral blood mononuclear cells with SEB significantly increased T_H1 and T_H2 pro-inflammatory cytokines in both

Figure 3 Effect of staphylococcal enterotoxins (SEs), IgE against staphylococcal enterotoxins (IgE-SEs), and eicosanoid release on the inflammatory network in upper airway diseases. (1) Binding of SEs to MHC-II in antigen-presenting cells (APCs) and to the TCR on T cells results in the activation of both T_H1 and T_H2 cells. (2) T_H2 cytokine IL-5 induces eosinophil activation and survival. Activation of eosinophils leads to the release of RANTES, eotaxin, LTB_4 , and CysLTs ($LTC_4/D_4/E_4$). RANTES and eotaxin are potent chemoattractants and contribute to the further recruitment of eosinophils and neutrophils to the inflamed tissue. CysLTs are potent eosinophil activators and greatly contribute to the release of eosinophil cationic protein, chemokines, and hence CysLTs (autocrine loop) contributing to chronic cell activation. (3) LTB_4 is an important chemoattractant and activator of neutrophils, which can also interact and contribute to eosinophilic inflammation. (4) At the same

time, mast cells may be activated by local IgE-SEs resulting in their degranulation and release of PGD_2 and CysLTs promoting T_H2 activation and recruitment and eosinophil inflammation. (5) T_H1 cytokine IFN- γ has the capacity to induce the expression of MHC-II molecules in nasal tissue fibroblasts. This allows SEs to bind to these cells and blocks COX-2 and PGE_2 production, cell growth and increase cell migration influencing in this way tissue remodeling. (6) Finally, the activation of nasal epithelial cells (SEs may be one of the triggers) leads to the production of LXA_4 , which attenuates neutrophil activation and recruitment, but also may induce changes in Ca^{2+}/Cl^- channels promoting edema. From the same pathway, epithelial cells can also release 15-(S)-HETE, which promotes neutrophil recruitment and activation. COX, cyclooxygenase-1; 15-(S)-HETE, 15-Hydroxyeicosatetraenoic acid; SEs, *Staphylococcus aureus* enterotoxins

AERD and non-AERD groups compared to controls (70). This response may be related to a baseline deficiency of Foxp3 and/or to the up-regulation of the tumor necrosis factor receptor superfamily member 18 (TNFRS18-L) on monocytes/dendritic cell precursors observed in the NP-asthmatic patients regardless of the clinical occurrence of AERD (70).

The data underline that staphylococcal SAgS contribute to airway inflammation in both upper and lower airways by influencing a large number of molecular inflammatory

mechanisms as shown in Fig. 3; however, there are no arguments yet for a specific role of SEs in AERD.

Staphylococcal SAgS and eicosanoid metabolism

There is only little evidence that staphylococcal enterotoxins may influence eicosanoid biosynthesis in humans. In 1995, Mehindate et al. (71) showed that triggering of the MHC-II by SEs in human fibroblast-like synoviocytes induced the expression of extracellular matrix complex-

related molecules and this event was mediated by the induction of COX-2 enzyme and the subsequent production of PGE₂. Later, Yamamura et al. (72) demonstrated that synovial fibroblasts can function as accessory cells for SAg-induced T-cell activation by influencing the synthesis of stromelysin, IL-6, IL-8, and PGE₂. This capacity of SEs to regulate fibroblast function by acting via MHC-II was later extrapolated to the upper airways. We demonstrated that incubation of nasal tissue fibroblasts with the T_H1 cytokine IFN- γ induced the expression of MHC-II molecules allowing SEs bind to the cells. This resulted in a significant down-regulation of PGE₂ production, COX-2 and EP2 mRNA expression and influenced cell growth and migration (Fig. 3), which may contribute to the exacerbation of inflammation in the nasal mucosa by mainly affecting tissue remodeling (73). This may be explained by the fact that with the down-regulation of PGE₂, the potential of inhibiting the pro-inflammatory effect of SEB as demonstrated by Okano et al. decreases (74). In this study, SEB stimulation of dispersed nasal polyp cells resulted in a significant increase in IL-5, IL-13, RANTES cytokine production, and eosinophil number, which was abolished after the administration of PGE₂ via an EP2 receptor- and EP4 receptor-mediated mechanism (74). Furthermore, in 2001, Wehner et al. (75) showed that stimulation of basophils from patients with atopic eczema with SEs resulted in the release of histamine and LTs, indicating a role of these toxins as possible allergens in this group of patients. So far, there is no evidence that SEs can directly influence the LTs regulatory pathway in the airways. However, these enterotoxins can induce the synthesis of IL-5, which may induce the activation of ALOX5 leading to CysLTs synthesis and hence to the recruitment of activated eosinophils to the site of inflammation (43). In upper airways, concentrations of CysLTs, LTB₄, and LXA₄ are up-regulated and correlated with the markers of eosinophil activation and survival (ECP and IL-5) in nasal polyp tissue from patients exhibiting an immune response to *S. aureus* enterotoxins as compared with tissue from those who were negative for IgE-SEs (18).

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Conclusion

Chronic rhinosinusitis is considered a multifactorial disease involving several immunological mechanisms that may act on their own or in combination. In the last years, evidence has been collected demonstrating the role of an imbalance in the synthesis of eicosanoids in the development and chronicity of the disease. This imbalance is based on a tissue cell deficiency in the production of anti-inflammatory molecules such as prostaglandin E₂ and lipoxins in contrast to high levels of pro-inflammatory mediators such as CysLTs, prostaglandin D₂, and 15-HETE. This imbalance leads to a severe eosinophil inflammation and changes in the cellular electrophysiology contributing to airway hyper-responsiveness mainly observed in patients with CRS and nasal polyps, and even more aggravated in asthmatic and aspirin-intolerant patients. Furthermore, staphylococcal enterotoxins have gained special attention as amplifying factors of airway inflammation. These molecules influence the local T-helper immune response in nasal polyp patients and have been considered a determinant factor associated with severe disease. Still extensive studies have to be carried out in order to elucidate the mechanism regulating eicosanoid and immune response to SAg in airway diseases. However, they are currently considered a major target for new diagnostic and therapeutic approaches, which may have relevant clinical and economic implications.

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Conflicts of interest

All authors declare no conflict of interests relevant to this manuscript.

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