Current perspectives

Pathogenesis of chronic rhinosinusitis: Inflammation

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Chronic rhinosinusitis (CRS) is a heterogeneous group of inflammatory diseases of the nasal and paranasal cavities either accompanied by polyp formation (CRSwNP) or without polyps (CRSsNP). CRSsNP and CRSwNP are prevalent medical conditions associated with substantial impaired quality of life, reduced workplace productivity, and serious medical treatment costs. Despite recent research evidence that contributes to further unveiling the pathophysiology of these chronic airway conditions, the cause remains poorly understood and appears to be multifactorial. A diverse spectrum of alterations involving histopathology, inflammatory cell and T-cell patterns, remodeling parameters (eg, TGF-β), eicosanoid and IgE production, microorganisms, and epithelial barrier malfunctions is reported in the search to describe the pathogenesis of this heterogeneous group of upper airway diseases. Furthermore, novel evidence indicates considerable heterogeneity within the CRSwNP subgroup determining the risk of comorbid asthma. The characterization of specific disease subgroups is a challenging scientific and clinical task of utmost importance in the development of diagnostic tools and application of individualized treatments. This review focuses on recent evidence that sheds new light on our current knowledge regarding the inflammatory process of CRS to further unravel its pathogenesis. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: *Chronic rhinosinusitis, nasal polyps, remodeling, inflammation,* Staphylococcus aureus*, IgE, eicosanoids*

Abbreviations used

CRS:	Chronic rhinosinusitis
CRSsNP:	Chronic rhinosinusitis without nasal polyps
CRSwNP:	Chronic rhinosinusitis with nasal polyps
ECM:	Extracellular matrix
ECP:	Eosinophil cationic protein
EP2 receptor:	E-prostanoid-2 receptor
PGE_2:	Prostaglandin E_2
SE:	*Staphylococcus aureus* enterotoxin
SEB:	*Staphylococcus aureus* enterotoxin B
SE-IgE:	*Staphylococcus aureus* enterotoxin–specific IgE
Treg:	Regulatory T

Because inflammation of the nasal and sinus mucosa often coexist, the current consensus terminology is "rhinosinusitis." The disease status is further defined to be chronic when symptoms persist for more than 12 weeks with no complete resolution (chronic rhinosinusitits [CRS]). However, because this clinical consensus term is not intended to describe or suggest an underlying cause but just fits most accurately the clinical presentation of the condition or conditions to be defined, it is not excluded that the pathogenesis of the anatomic manifestations of rhinitis and sinusitis might be distinct. A recent study illustrated that the inflammatory mediator profile in the nasal mucosa of patients with CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRWwNP) follows the profile found in sinus mucosa from the respective patient groups, confirming that rhinitis and sinusitis can indeed be regarded as one disease entity and thus further supporting the use of the term rhinosinusitis.[1]

The question remains whether CRSwNP and CRSsNP represent a disease spectrum or manifest as different diseases that normally develop separately and maintain their characteristics throughout the lifetime. A part of the answer might be given by characterizing these pathologies on the basis of the expression of inflammatory and remodeling patterns. Indeed, the evaluation of inflammatory cell profiles (eosinophils vs neutrophils), the presence of differentiated T-effector cells (T_H1, T_H2, and T_H17) and regulatory T (Treg) cells, and the characterization of remodeling processes, such as fibrosis or edema formation, might provide tools to identify distinct disease entities within the group of chronic sinus diseases. This review will briefly summarize the most important and recent findings that potentially have a significant effect on the knowledge of the cause and clinical understanding of CRSsNP and CRSwNP, as well as on the research perspectives for future drug development.

REMODELING: FIBROSIS VERSUS EDEMA

Histologically, CRSsNP is characterized by fibrosis, basement membrane thickening, goblet cell hyperplasia, subepithelial edema, and mononuclear cell infiltration, whereas CRSwNP is characterized by an intense edematous stroma with albumin deposition, formation of pseudocysts, and subepithelial and perivascular inflammatory cell infiltration. Remodeling is a dynamic process in both health and disease that balances extracellular matrix (ECM) production and degradation, which is regulated by diverse mediators among which TGF-β takes a central role. In addition to being a key factor in the generation or the deficit of Treg cells, TGF-β is also a critical factor implicated in the remodeling process in the airways through the attraction and induction of proliferation of fibroblasts and the upregulation

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of ECM synthesis. In a recent study investigating the involvement of the remodeling process in patients with CRS, we reported that TGF-β1 and 2 protein concentrations, TGF-β receptor I and III mRNA expression, and the number of activated pSmad 2–positive cells were significantly higher in patients with CRSsNP versus control subjects. In contrast, in patients with CRSwNP, TGF-β1 protein concentration, TGF-β receptor II and III mRNA expression and the number of activated pSmad 2–positive cells were significantly lower versus control subjects.[2] Although it was described that the number of patients yielding measurable TGF-β mRNA levels were lower in both patients with CRSsNP and patients with CRSwNP versus control subjects,[3] the reported data for TGF-β on protein level are in good agreement with the known morphologic and remodeling differences between both clinical entities.[2] Indeed, the upregulation of the TGF-β signaling pathway in patients with CRSsNP and its downregulation in patients with CRSwNP on the protein level are reflected by edema formation and a lack of collagen production in patients with CRSwNP and excessive collagen deposition associated with fibrosis in patients with CRSsNP (Fig 1).[2] TGF-β signaling also contributes to the regulation of expression of matrix metalloproteinases and their natural tissue inhibitors (tissue inhibitors of metalloproteinases), the imbalance of which allows ECM degradation and albumin deposition, contributing to the edema.

In contrast to past investigations focusing on inflammatory differences, which will be discussed below, recent evidence from studies comparing patients with CRSsNP and patients with CRSwNP among white and Asian populations showed that the above-stated remodeling patterns on the protein level (alterations in TGF-β protein concentrations, levels of matrix metalloproteinase 9 proteins, and total collagen deposition) are reasonably conserved,[2,4] indicating that TGF-β proteins and their signaling might be universally applicable markers to differentiate the distinct CRS entities. In essence, we therefore suggest TGF-β protein as a key differentiation marker discriminating CRSsNP and CRSwNP. In view of the consistency of the remodeling patterns, we propose those protein markers as an innovative approach for CRS disease classification. In line with this, we recently observed an upregulation of TGF-β and an increase in collagen deposition in patients with early-stage CRSsNP without any sign of inflammation (unpublished data).

INFLAMMATORY CELL PROFILES AND T-CELL PATTERNS

Patients with CRSsNP and CRSwNP are also described to be immunologically distinguishable on the basis of the expression of inflammatory mediators. Among white subjects, CRSwNP was initially associated with a typical T_H2-skewed eosinophilic inflammation with high IL-5 and eosinophil cationic protein (ECP) concentrations in the polyps, whereas CRSsNP was characterized by a T_H1 milieu with increased levels of IFN-γ in the inflamed sinus mucosa and low ECP/myeloperoxidase ratios.[5] CRSwNP furthermore consistently demonstrated a clear-cut upregulation of the T-cell activation marker soluble IL-2 receptor α and a significant downregulation of forkhead box protein 3 expression and TGF-β1 protein content versus control subjects.[6,7] The low TGF-β1 levels in nasal polyps can be functionally related to a decreased Treg cell activity, which could indeed be backed up by the reported low levels of forkhead box protein 3 expression in patients with CRSwNP (Fig 1).[7] Kim et al[8] functionally

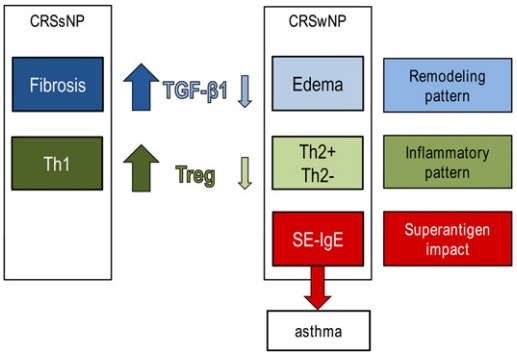

FIG 1. Phenotyping of CRS. CRSsNP and CRSwNP are regarded as distinct clinical entities based on diverse inflammatory and remodeling parameters. *Th2+*, IL-5 positive, Th2-skewed tissues; *Th2−*, IL-5 negative Th2-skewed tissues; *SE-IgE,* IgE antibodies to *Staphylococcus aureus* enterotoxins (SE). *Arrows* do not suggest causality.

confirmed an attenuated migration of Treg cells in subjects with CRSwNP, which might explain the reduced Treg levels in patients with CRSwNP. Increased expression of T-box transcription factor T-bet or GATA-3 in nasal polyp tissue indicates that the deficient Treg cell function in patients with CRSwNP is accompanied by an increased activity of T_H cells.[6,7] In contrast, CRSsNP demonstrates no deficit in Treg cell numbers[7] and migration capacity[8] and displays a much less severe inflammatory mucosal reaction (Fig 1).[7]

Although the above-described universally applicable inflammatory and remodeling features differentiating CRSwNP from CRSsNP might give the impression that nasal polyposis is a homogenous disease state, recent reports show the opposite. Considerable heterogeneity within the CRSwNP subgroup can be observed, as was evidenced by reports from Asian countries showing that nasal polyps also can be neutrophilic and might be treated with macrolide antibiotics in contrast to the eosinophilic inflammation in white subjects in whom the recommended treatment consists of topical corticosteroids. Indeed, in contrast to white subjects, it was reported that in Chinese patients CRSwNP demonstrated a T_H1/T_H17 polarization with low ECP levels biased toward a neutrophilic inflammation. Although both CRSwNP groups were comparable in terms of symptoms, computed tomographic scan and nasal endoscopy results, asthma comorbidity was significantly higher in white subjects.[6] These geographic differences were recently confirmed once more: although 83% of polyps from white subjects expressed IL-5 protein and more than 50% were characterized as eosinophilic (ECP/myeloperoxidase ratio, >1), in the Chinese group only 16% expressed IL-5 protein and less than 10% were eosinophilic.[9] Whether this variation is due to genetic or environmental differences remains unclear and needs to be studied.

Considerable heterogeneity can also be observed within one ethnic entity of the population with CRSwNP. Indeed, it was recently demonstrated that the 3 major T-effector cell cytokines described until recently (IFN-γ, IL-5, and IL-17) can coexist in the upper airway mucosa within 1 patient; their pattern in nasal polyp tissue affects and differentiates mucosal inflammation, demonstrating a mixed eosinophilic/neutrophilic activation pattern when present concurrently in these subjects, whereas polyp tissues from other subjects did not express any of the key T-cell cytokines. Next to the previously described predominant T_H17 effector cells in Asian patients with polyps, yielding a

predominance of neutrophil granulocytes,[6] IL-17 was shown also to be expressed in individual white patients with nasal polyps. We distinguished IL-$5^{+/-}$, IL-$5^{+/-}$/IL-17^{+}, IL-$5^{+/-}$/INF-γ^{+}, and IL-5^{+}/IL-17^{+}/INF-γ^{+} nasal polyp subgroups, allowing us to identify high IL-5–containing tissues with either a lack of IL-17, a lack of IFN-γ, or both as a high-risk group within the CRSwNP family to develop the most severe eosinophilic inflammation.[9] The same study further supported the concept of the united airways by showing that the presence of IL-5 and IgE antibodies to staphylococcal enterotoxins in human nasal polyps was associated with comorbid asthma. The latter, together with the low frequency of IL-5^{+} nasal polyps in Asian subjects, is indeed in agreement with the fact that asthma comorbidity was found to be significantly less frequent in Asian than in white patients with CRSwNP.[6,9] The analysis of a specific inflammatory cytokine pattern might be necessary to adequately phenotype individual patients with CRSwNP with respect to prognosis and treatment.

MICROORGANISMS AND COMPROMISED EPITHELIAL BARRIER FUNCTION

Staphylococcus aureus is a frequent colonizer of the nasal cavity in white subjects, with an average persistent carrier rate of 20% to 30% of adults. An increased colonization rate of *S aureus* was demonstrated in patients with CRSwNP (63.6%) but not in patients with CRSsNP (27.3%) versus control subjects.[10] Invasion of the epithelium by *S aureus* is another phenomenon seen predominantly in patients with CRSwNP, as was confirmed by Sachse et al,[11] who reported that regardless of an intracellular or extracellular localization in the epithelium, *S aureus* is capable of inducing IL-6 synthesis *in vitro* and might in this way contribute to the T_H2 cytokine pattern in patients with CRSwNP. *S aureus* furthermore secretes *Staphylococcus aureus* enterotoxins (SEs), which elicit a massive inflammatory reaction resulting from a polyclonal activation of T and B lymphocytes. This feature of SEs, known as superantigens, is independent of the specific adaptive immune response. *Staphylococcus aureus* enterotoxin B (SEB) was described to further shift the cytokine pattern in nasal polyps toward T_H2 cytokines, amplifying eosinophilic inflammation, and to further disfavor the Treg cytokines IL-10 and TGF-β1.[12] Moreover, *S aureus*–derived protein A induces a significant increase in histamine levels, leukotriene numbers, and prostaglandin D_2 levels, indicating mast cell activation.[12] *S aureus* superantigens also can induce the formation of polyclonal IgE directed against multiple inhalant allergens, which was suggested to be implicated in maintaining a continuous activation of mast cells as part of the pathomechanism by which SEs affect mucosal inflammation.[13] Recently, the presence of IL-5 and IgE antibodies to *Staphylococcus aureus* enterotoxin–specific IgE (SE-IgE positivity) in human nasal polyps was shown to be associated with an increased risk of patients having asthma comorbidity, indicating the decisive role of staphylococcal superantigens in amplifying and aggravating airway disease[9]: the likelihood of having comorbid asthma was about 6 times higher when IgE antibodies to SEs were present in mucosal tissue of patients with CRSwNP (Fig 1). Furthermore, SE-IgE positivity was linked to increased levels of total IgE and ECP, suggesting strong proinflammatory and IgE-inducing effects of SEs within the nasal tissue.[9] Although SEs clearly have an amplifying and modulating role in airway disease, evidence for a direct causal relationship of *S aureus* in patients with CRS is lacking.

Also, fungi have frequently been hypothesized to be implicated as a disease generator/modulator in patients with CRS. Although fungi are described to be present in the noses and sinuses of nearly all patients with CRS, no significant difference in fungal isolation in comparison with healthy control subjects could be detected in multiple studies.[14] Moreover, Okano et al[15] recently showed through *ex vivo* functional evidence that fungal antigens (*Aspergillus*, *Alternaria*, and *Candida* species) are less capable of inducing eosinophilia-associated cellular responses in nasal polyps compared with SEB. Furthermore, no significant correlations were detected with regard to the amount of IL-5, IL-13, or RANTES produced after exposure to fungal extracts and various pathophysiological features, including nasal polyp eosinophilia, peripheral blood eosinophilia, or radiologic severity of sinusitis.[15]

Microorganisms are under physiological conditions readily eliminated at the mucosal lining of the upper airways without involvement of the adaptive immune system. It was therefore hypothesized that an impaired epithelial immune barrier function might be a causative mechanism in patients with CRS[16]: deficiencies in the immune barrier function might compromise the pathogen-host interaction and make the sinonasal mucosa more susceptible to antigenic exposure, leading to chronic inflammation. Epithelial damage has indeed been observed in patients with CRSwNP, whereas genetic deficiencies, environmentally induced damage, or both in epithelial repair mechanisms can be associated with both forms of CRS.[16] Alterations in mucosal macrophages located at the epithelial barrier on the interface with the external environment might contribute to the immune barrier dysfunction in patients with CRSwNP. Indeed, compared with control subjects and patients with CRSsNP, the sinonasal mucosa of these patients was reported to significantly show more alternatively activated M2 macrophages, which are immunosuppressive, support a T_H2 bias, and might allow intracellular survival of bacteria and viruses.[17] Moreover, the increased presence of *S aureus* in patients with CRSwNP could be partly explained by an inefficiency of the phagocytic system in the sinomucosal tissue of these patients.[17] Conversely, in a study using a murine model of subcutaneous catheter-associated biofilm infection, the authors suggested that *S aureus* biofilm *per se* programmed macrophages toward an alternatively activated M2 phenotype.[18] Regardless of the exact initiator, decreased phagocytosis by an M2-skewed macrophage phenotype in patients with CRSwNP potentially contributes to the persistence of chronic inflammation in patients with CRSwNP.

ROLE OF EICOSANOIDS AND THEIR RECEPTORS

Patients with CRSwNP typically demonstrate increased levels of proinflammatory cysteinyl leukotrienes and a downregulation of cyclooxygenase-2 (COX-2) accompanied by reduced levels of prostaglandin E_2 (PGE_2),[19] the latter being considered an anti-inflammatory metabolite that might influence Treg cell–mediated mechanisms. Indeed, in addition to SEs, eicosanoids are important amplifiers and regulators of inflammation in patients with airway diseases. Moreover, both might have a possible reciprocal influence on each other. In cultured inferior turbinate fibroblasts obtained from healthy control subjects, SEB treatment significantly downregulated PGE_2, COX-2, and E-prostanoid-2 (EP2) receptor mRNA expression, pointing to an effect of

staphylococcal superantigens on eicosanoid metabolism in upper airway tissue.[20] Very similarly, others also reported moderate PGE_2 production and a low COX-1/2 and EP2 receptor expression after IL-1β exposure of fibroblasts derived from nasal polyps compared with that seen in fibroblasts from control inferior turbinates.[21] Conversely, PGE_2 was reported to significantly and dose dependently inhibit SEB-induced IL-5, IL-13, and RANTES production by dispersed nasal polyp cells in the presence of the COX inhibitor diclofenac. Because the effect of PGE_2 was mimicked by a selective prostanoid EP2 receptor agonist, it was suggested that PGE_2, through EP2 receptors, inhibits the pathogenesis of SEB-induced eosinophilic inflammation.[22] Staphylococcal enterotoxins can thus have an additional amplifying role in upper airway disease by inhibiting the anti-inflammatory effect that PGE_2 might have through EP2 receptor activation. Because the latter mechanism in dispersed nasal polyp cells did not occur in the absence of diclofenac, it can be suggested that endogenous levels of constitutively produced PGE_2 are to some extent able to suppress the inflammatory response. Taking the latter together with the previously reported low levels of PGE_2 in patients with CRSwNP,[19] which might be related to the high colonization rate of *S aureus*,[20] the altered prostanoid pathways could equally be hypothesized to be at the basis of the cause of CRSwNP.

PERSPECTIVES ON INNOVATIVE THERAPEUTICS FOR UPPER AND LOWER AIRWAY CONDITIONS

There currently exists no effective therapeutic drug for CRSsNP, and severe CRSwNP that is often complicated by severe asthma, is insufficiently controllable by either repeated sinus surgery or topical and oral corticosteroids. Innovative individualized therapeutic approaches need to be tailored for each specific subgroup of patients with CRS.

On the basis of our currently limited knowledge, a first possible selective target that might provide a basis for a novel therapeutic approach in the management of eosinophilic airway diseases, such as CRSwNP, could be found in the prostanoid receptor family. Selective prostanoid EP2 agonists could have protective effects through counteracting SE-induced proinflammatory responses.[19-21]

Second, innovative therapies in CRSwNP might furthermore be based on the knowledge of T-cell signatures and relevant cytokines and might target IL-5, IL-4, and/or IL-13. They also might aim to suppress the proinflammatory effect of polyclonal IgE antibodies (extremely high mucosal IgE concentrations covering hundreds or even thousands of allergens, which all contribute to the chronic activation of mucosal mast cells)[9] by either antagonizing IgE with anti-IgE humanized antibodies or by interfering with B-cell activation, such as through IL-21 or B-cell activating factor antagonism or related principles. Of those approaches mentioned, the anti–IL-5 antibodies reslizumab[23] and mepolizumab have been tested under clinical conditions already, and anti-IgE (omalizumab) also might have great potential. However, because responder rates to the above-mentioned treatments will be in the range of 50% to 80% of patients, depending on the clinical phenotypes, identification of specific disease subgroups within the broad concept of CRS classification and biomarker identification will be important and challenging tasks for future research, which need to be translated into clinics.

Most importantly, the insights into upper airway disease might equally provide new lines of thinking for lower airway treatments; it is very likely that similar principles are also valid for the lower airways of patients with CRS with comorbid asthma and even for lower airway conditions independent of sinus disease. First evidence has been provided recently in a group of patients with severe refractory asthma versus patients with nonsevere asthma, confirming the effect of SE-IgE on total IgE concentrations and lung function parameters.[24] Patients with polyclonal IgE and with SE-IgE antibodies serving as markers of the staphylococcal superantigen effect are at increased risk of comorbid, potentially severe, late-onset asthma (Fig 1).[9] Consequently, CRS not only needs to be diagnosed and phenotyped to optimize future research and therapy by the rhinologist but also from the perspective of a chest physician.

CONCLUSION

A diverse set of immunologic parameters, such as effector T-cell signatures, eosinophilic versus neutrophilic inflammation patterns, and remodeling profiles clearly allow CRSsNP and CRSwNP to be discerned (Fig 1). These parameters are therefore also potentially implicated in the cause or pathogenesis of the respective disease entities. The term "chronic rhinosinusitis" refers to an umbrella for sinus diseases, which in fact are distinct in inflammatory and remodeling patterns: CRSsNP and CRSwNP can be recognized as separate disease entities based on inflammatory and remodeling profiles (Fig 1). These patterns might affect the prognosis, asthma comorbidity (Fig 1), appropriate surgical approach, recurrence rates, and certainly the pharmacologic management including biological agents. Although inflammatory cell and mediator patterns can vary considerably based on geographic coordinates and even from patient to patient within the CRSwNP disease group, remodeling patterns are reasonably conserved. In view of the consistency of these remodeling patterns, we propose those markers as an innovative approach for CRS disease classification. The remodeling mediator TGF-β and its signaling might indeed be a key marker that discerns CRSsNP from CRSwNP (Fig 1).

CRSsNP in the vast majority of patients shows a T_H1-skewed inflammatory response, whereas the CRSwNP group is rather heterogeneous. Disease severity and comorbidity in patients with CRSwNP are influenced by various interfering factors. The severity of inflammation in T_H2-biased patients with CRSwNP might be amplified by SEs acting as superantigens through polyclonal T- and B-cell activation, leading to mucosal "local" IgE formation in patients with CRSwNP. This subgroup of patients with nasal polyps is at risk of comorbid severe asthma (Fig 1). Appropriate diagnostic tools and algorithms need to be developed to translate these findings into daily practice.

Although the immunologic diversity in inflammatory parameters seems to stand in contrast to the universal clinical presentation of nasal polyps, the knowledge on the exact disease phenotype is of great importance in the development and application of highly individualized therapeutics. New therapeutic approaches indeed need to be tailored to each specific subgroup of patients with CRS. Therefore identification of specific disease subgroups within the broad concept of CRSsNP/CRSwNP classification, clustering cause, and biomarker identification will be important and challenging tasks for future research. On the basis of new insights, possible selective targets that might provide a basis for a novel therapeutic approach in the management of eosinophilic airway diseases, such as CRSwNP, could be found in the prostanoid

receptor family and humanized antibody treatments primarily targeting T_H2-biased and SE-IgE–positive subjects.

In conclusion, the analysis of a specific inflammatory cytokine pattern is necessary to adequately phenotype individual patients with CRS with respect to prognosis and novel treatments.

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