Advances in rhinitis and rhinosinusitis in 2015

Claus Bachert, MD, PhD,[a,b] and Elien Gevaert, PhD[a] *Ghent, Belgium, and Stockholm, Sweden*

The last year has seen great progress in the understanding of upper airway disease and in its management. For allergic rhinitis, authors focused on the prediction of and effect on the natural course of disease. New evidence was published for the disease-modifying effect of allergen immunotherapy in terms of avoidance of new sensitizations and prevention of asthma in either randomized or real-life studies. Specifically, for patients with house dust mite allergies, which are often underestimated and difficult to diagnose, the efficacy of SQ house dust mite sublingual immunotherapy tablets has been demonstrated in patients with allergic rhinitis and asthma. For the first time, allergen immunotherapy significantly reduced asthma exacerbations. In patients with chronic rhinosinusitis, a novel endotyping approach purely based on T helper cell biomarkers has been developed and has shown clinical relevance through associations with asthma comorbidity and recurrence after surgery. Severe nasal polyposis with high risk for asthma comorbidity and disease recurrence is characterized by type 2 inflammatory patterns, including IgE antibodies to staphylococcal superantigens; several studies using biologic agents have targeted exactly this spectrum of mediators. This goes in parallel with new knowledge on even more type 2 mediators derived from epithelial cells, which will expand the number of possible candidates for innovative intervention. (J Allergy Clin Immunol 2016;138:1277-83.)

Key words: *Allergic rhinitis, allergen components, allergen-specific immunotherapy, house dust mite, chronic rhinosinusitis, endotype, type 2 cytokines*

In the past year, exciting new knowledge was achieved, increasing our understanding in allergic rhinitis (AR), including its causal management approach immunotherapy, and chronic rhinosinusitis related to endotypig and disease pathomechanisms. We here summarize (Table I) these findings and discuss their impact on the field.

Abbreviations used

AERD:	Aspirin-exacerbated respiratory disease
AFRS:	Allergic fungal rhinosinusitis
AIT:	Allergen-specific immunotherapy
AR:	Allergic rhinitis
BAMSE:	Swedish abbreviation for "Children, Allergy, Milieu, Stockholm, Epidemiology"
CRSsNP:	Chronic rhinosinusitis without nasal polyps
CRSwNP:	Chronic rhinosinusitis with nasal polyps
EXCELS:	Epidemiologic Study of Xolair: Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma
GR:	Glucocorticoid receptor
HDM:	House dust mite
ICS:	Inhaled corticosteroid
MUC1-CT:	Cytoplasmic tail of mucin 1
OSM:	Oncostatin M
PGD_2:	Prostaglandin D_2
Siglec:	Sialic acid–binding protein
SLIT:	Sublingual immunotherapy
TSLP:	Thymic stromal lymphopoietin

ALLERGIC RHINOCONJUNCTIVITIS

After a substantial increase in the prevalence of atopic dermatitis, asthma, and allergy in Europe for 2 decades,[1] a recent study in Denmark and Sweden[2] using national registers demonstrated a stable incidence rate for atopic dermatitis; an increase in asthma incidence until 2006 that then stabilized, at least in Denmark; and a decrease in allergic rhinoconjunctivitis incidence in both countries. One third of all 5-year-old children were affected with at least 1 of the conditions, but there was evidence that this number would not further increase. This situation might be different from what we see in developing countries in which allergies still are on the increase.[3]

Prediction of allergic disease

Great interest goes to the prediction of allergic disease and IgE formation in children. Allergen components can be differentiated into protein families; by using an allergen chip in a population-based birth cohort, 112 component-specific IgE responses were related to asthma, eczema, and hay fever.[4] About half of the allergens clustered into 3 component groups, consisting of components from plants, mites, animals, and fungi: component group 1 (27 components from 8 plants) was associated with AR, component group 2 (7 components from mites) was associated with rhinitis and asthma, and component group 3 (27 components from plants, animal, and fungal origin) was associated with asthma and low lung function parameters (FEV_1). No association

From [a]the Upper Airways Research Laboratory and ENT-Department, Ghent University Hospital, and [b]the Division of ENT Diseases, CLINTEC, Karolinska Institute, University of Stockholm.

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Corresponding author: Claus Bachert, MD, PhD, Upper Airways Research Laboratory and ENT-Department, Ghent University, De Pintelaan 185, 9000 Ghent, Belgium. E-mail: Claus.Bachert@ugent.be.

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TABLE I. Key advances in allergic rhinitis and chronic rhinosinusitis

- Component-resolved diagnosis might improve the prediction of future allergy in young children.
- There is little possibility to interfere with the natural course of disease through early-life environment or lifestyle changes.
- For the first time, evidence for the reduction of asthma risk by using AIT was achieved in adults in a real-life setting.
- High-dose HDM extract in infants less than 1 year of age at high risk of atopy significantly reduced sensitization to any common allergen.
- General claims for AIT should be replaced by product-specific evaluations.
- Efficacy of HDM (SQ HDM) allergy tablets was demonstrated in a challenge chamber and a double-blind, placebo-controlled randomized phase III trial in adults with moderate-to-severe HDM-induced AR.
- SQ HDM tablet treatment in adults with HDM allergy–related asthma improved time to first asthma exacerbation in a period of ICS reduction.
- A 5-grass-pollen tablet demonstrated efficacy for up to 2 years after treatment in a double-blind, placebo-controlled, randomized phase III trial.
- CRS consists of multiple groups of biological endotypes, which are defined by distinct pathophysiologic mechanisms.
- Endotypes can demonstrate differences in the natural course of disease, prognosis of recurrence, risk of comorbid asthma, and responsiveness to different treatments.
- Type 2 inflammation is associated with recurrence of disease after surgery in patients with CRSwNP.
- Biologics, such as omalizumab and dupilumab, have demonstrated efficacy in proof-of-concept studies in patients with CRSwNP.
- The epithelium-derived cytokines TSLP, IL-25, and IL-33 play an important role in innate type 2 reactions.
- T_H2 cytokines, and IL-13 more specifically, influence mucociliary clearance through induction of epithelial ion transport proteins.
- Eosinophils gain attention as central effector cells in both the innate and adaptive immune systems.

with eczema was observed. Similarly, component-resolved diagnosis might improve the prediction of future allergy in young children, as was shown using the BAMSE birth cohort.[5] IgE reactivity to the pathogenesis-related class 10 protein family, including Bet v 1 and other proteins, at 4 years of age was associated with AR to birch pollen and its severity at 16 years of age.

The longitudinal development of IgE patterns was also the subject of a study investigating the evolution of IgE responses to allergenic components of timothy grass and dust mites during childhood.[6] For grass pollen, there were 3 sensitization patterns: no/low sensitization, early-onset sensitization, or late-onset sensitization. The early-onset pattern was associated with asthma and diminished lung function, whereas the late-onset pattern was associated with rhinitis. For house dust mite (HDM) sensitization, it was important to note which allergens were included: no/low sensitization and sensitization to group 1 allergens, group 2 allergens, and both. Children with sensitization to both group 1 and 2 allergens had the highest odds ratios for asthma (odds ratio, 7.15; 95% CI, 3.80-13.44) and were the only group significantly associated with comorbid asthma, rhinitis, and eczema (odds ratio, 5.91; 95% CI, 2.01-17.37). Among children with wheezing, those with this pattern only had a significantly higher risk of severe exacerbations. Thus the analysis of allergen components might help predict the natural course of allergic airway diseases in the future.

Can we change the natural course of disease?

The question then arises whether we can also prevent those patterns by changing the early-life environment or lifestyle. Using the Multicenter Allergy Study cohort, risk factors for allergic rhin(oconjunctiv)itis up to age 20 years were analyzed.[7] The risk of AR was higher with a parental history of AR, early allergic sensitization, eczema within the first 3 years of life, male sex, and birthday in summer or autumn were independent predictors of AR up to age 20 years. However, none of the socioeconomic, environmental, lifestyle, pregnancy, or birth-related factors were associated with AR at age 20 years. This study indicated little possibility to interfere with the natural course of disease by early-life environment or lifestyle changes.

ALLERGEN-SPECIFIC IMMUNOTHERAPY

Allergen-specific immunotherapy (AIT) is considered the only treatment option for allergic airway diseases, specifically for AR but increasingly also for asthma. AIT has been demonstrated to have a disease-modifying effect, which translates into long-term clinical improvements even after AIT is discontinued.[8] Allergen immunotherapy also has the potential to prevent the onset, progression, or both of asthma and reduce or slow down neosensitizations to other allergens.[9,10] In a prospective, randomized, double-blind, placebo-controlled proof-of-concept study involving 111 infants less than 1 year of age at high risk of atopy (≥2 first-degree relatives with allergic disease) but with negative skin prick test responses to common allergens, a high-dose HDM extract and appropriate placebo solution were administered orally twice daily for 12 months. The study showed a significant reduction in sensitization to any common allergen in the active (9%) compared with placebo (25%) treatment groups.[9]

For the first time, evidence for the reduction of asthma risk was also achieved in adults in a "real-life setting"[10]: using routine health care data from German National Health Insurance beneficiaries retrospectively, a consecutive cohort of 118,754 patients with AR but without asthma who had not received AIT in 2005 was identified. Two percent of those patients received AIT for about 3 years in 2006; asthma was newly diagnosed in 1.4% of all the patients from 2007-2012. The risk of incident asthma was significantly lower in patients exposed to AIT compared with those receiving no AIT in 2006 (risk reduction of 40%). Preventive effects were demonstrated for subcutaneous immunotherapy and native (nonallergoid) aqueous allergens; AIT tablets were not used in enough patients to test their preventive effects.

The recent year has seen excellent studies to support disease-modifying claims for AIT, which will be discussed here. At the same time, we moved away from the undifferentiated use of claims for every allergen preparation marketed that has never demonstrated evidence for efficacy and tolerability to product-specific evaluations.[11] The broad use of the abovementioned claims for all AIT products available is unjustified and should be replaced by a per-product appreciation of available evidence; this includes efficacy for the first year or 3 years of treatment or

2 years or more after discontinuation (disease-modifying effect). The preventive effect on asthma development can also not be associated with AIT in total. The comparison of subcutaneous immunotherapy and sublingual immunotherapy (SLIT) is not considered appropriate but should be replaced by product-specific evaluations independent of the route of application; a comparison of commercialized grass pollen immunotherapy products indicated comparable reductions in allergic rhinoconjunctivitis symptoms and supplemental medication use for SLIT tablets and subcutaneous immunotherapy in the first pollen season,[12,13] although direct head-to-head studies need to be performed. Considering the route of administration, efficacy and safety should be considered, stimulating the involvement of the patient in this decision.

AIT for HDM allergy

In the last year, several remarkable studies on AIT tablets for HDM allergy have been published. HDM is a major perennial allergen source and a significant cause of AR and allergic asthma. An overview[14] focused on the epidemiology of this important allergy and pointed out that HDM allergy can often remain undiagnosed and undertreated. The prevalence of HDM sensitization varies from 65 to 130 million persons in the general population worldwide, with up to 50% of asthmatic patients included. The domestic environment seems to be specifically important to understand the patient's exposure to the allergen (allergen load) but also to evaluate the opportunity for intervention measures. Inhaled mite allergens can be unusually virulent because they are able to activate both the adaptive and innate immune responses. HDM sensitizations are more frequently associated with both rhinitis and asthma than sensitization to any other frequent allergen. As a consequence, the need for treatment of HDM-induced asthma is high, but the lack of adequately studied products and the restrictions by AIT guidelines, which excluded uncontrolled asthma from AIT treatment, prevented the translation into practice.[15]

The efficacy and onset of action of an HDM SLIT tablet (MK-8237; ALK-Abelló, Hørsholm, Denmark) on HDM-induced AR and conjunctivitis was studied with the Vienna challenge chamber.[16] In a randomized, double-blind, placebo-controlled dose-ranging trial, adults with HDM-induced allergic rhinoconjunctivitis with or without asthma received tablet AIT or placebo for 24 weeks and were challenged over 6 hours in the chamber at screening and weeks 8, 16, and 24. Dose- and time-dependent improvements with MK-8237 versus placebo were observed from week 8 onward; at week 24, TNSS improvement relative to placebo was 48.6% (95% CI, 35.3% to 60.2%) with the marketed dosage, clearly exceeding the World Allergy Organization–established clinical efficacy criteria of greater than 20% improvement versus placebo. The drug was well tolerated. A phase III trial confirmed the efficacy and tolerability of the SQ HDM SLIT tablet (ALK-Abelló) in adults with moderate-to-severe HDM-induced AR, despite treatment with pharmacotherapy.[17] A randomized, double-blind, placebo-controlled trial including 992 adults investigated 2 dosages over 1 year. Both dosages demonstrated absolute reductions in total combined rhinitis scores; the statistically significant treatment effect was evident from 14 weeks of treatment onward. Efficacy for all key secondary end points was confirmed for the higher dose (12 SQ HDM), including statistically significant reductions in rhinitis symptoms and medication scores, the combined rhinoconjunctivitis score, and improved quality of life. The treatment was again well tolerated.

However, a new dimension in AIT was achieved when the SQ HDM SLIT tablet was studied in 834 adults with HDM allergy–related asthma that was not well controlled by inhaled corticosteroid (ICS) or combination treatment. The primary outcome was time to first moderate or severe asthma exacerbation during the ICS reduction period. In this study[18] the addition of HDM SLIT to maintenance medications improved time to first moderate or severe asthma exacerbation in a 6-month period of ICS reduction (ICS reduction by 50% for 3 months and then completely withdrawn for 3 months), with an absolute reduction of about 10%. The risk of an exacerbation with deterioration in asthma symptoms was reduced by 64% (95% CI, 0.42-0.96) for the 12 SQ HDM dose ($P = .03$), and a significant increase in allergen-specific IgG_4 levels was observed versus placebo. However, there was no significant benefit in terms of asthma control or asthma quality of life. There were also no reports of severe systemic allergic reactions, with oral pruritus being the most frequent adverse event. Because patients with AR often also have asthma and uncontrolled asthma often is considered a contraindication for immunotherapy, this study is of relevance to the indication of AIT in patients with AR. Even if asthma is not well controlled, HDM SLIT can be administered and be of benefit to patients with AR.

AIT for grass pollen allergy

Also, the 5-grass-pollen AIT tablet has proved short-term and sustained clinical efficacy in patients with allergic rhinoconjunctivitis. Adverse events were generally mild or moderate in severity and rarely led to treatment discontinuation. Adverse events also tend to decrease in frequency and severity over time and with repeated treatment.[19] In a randomized, double-blind, placebo-controlled, parallel-group, multicenter phase III trial, patients received daily verum or placebo treatment preseasonally and coseasonally.[8] The daily combined score (rhinoconjunctivitis total symptom score and rescue medication score) was assessed in a *post hoc* analysis in study years 4 and 5, which were treatment free. In adults with grass pollen–induced AR, the tablet therapy beginning 4 months before the pollen season and continuing to season's end demonstrated efficacy for up to 2 years after treatment.

Further interesting developments in AIT aim to confirm the usefulness of surrogate settings to replace the often unpredictable seasonal allergen exposure for dose-finding studies, such as environmental exposure chambers[20] and nasal or conjunctival provocation testing.[21] Because these settings can be used in registration studies, their validation is of utmost importance.

Another point of high interest is surrogate biomarkers for monitoring efficacy and tolerance after AIT; intracellularly labeled diamine oxidase (DAO) expression by basophils might merit further investigation.[22] Furthermore, new forms of AIT are constantly in development, such as a vaccine based on recombinant hypoallergenic derivatives of the major timothy grass pollen allergens Phl p 1, Phl p 2, Phl p 5, and Phl p 6 by using a peptide-carrier approach.[23] The efficacy and tolerability of those approaches need to be confirmed in the future.

CHRONIC RHINOSINUSITIS

Chronic rhinosinusitis (CRS) is a disease that can result in significant disability, affecting more than 10% of the

European[24] and American[25] populations. Although it mostly affects persons 30 years and older, it might affect 16-year-olds as well; 1.5% of Swedish adolescents had bothersome symptoms of CRS, affecting smell and quality of life.[26] Immunoglobulin subclass deficiencies and specific antibody deficiencies might be more prevalent in patients with recurrent CRS than appreciated thus far.[27,28]

CRS was frequently considered "one disease" in the past; however, the PRACTALL document of the European and American academies clearly pointed to the need of further differentiating or "endotyping" the disease.[29] Clinical phenotypes do not provide full insight into underlying cellular and molecular pathophysiologic mechanisms of CRS, and several phenotypes can show the same endotype; for example, allergic fungal rhinosinusitis (AFRS), aspirin-exacerbated respiratory disease (AERD), and eosinophilic bilateral nasal polyps are all type 2 immune reactions. CRS consists of multiple groups of biological endotypes, which are defined by distinct pathophysiologic mechanisms characterized by corresponding biomarkers. Those endotypes might demonstrate differences in the natural course of disease and prognosis in terms of recurrence after surgery and risk of comorbid asthma but also in responsiveness to different treatments, including topical intranasal corticosteroids, surgical interventions, and biological agents. For example, noneosinophilic nasal polyps, which are more prevalent in Asia compared with Europe or the United States, do not show the same response to topical and oral glucocorticosteroids as eosinophilic polyps.[30,31] In addition, different antibiotics, such as macrolides, demonstrate better efficacy in neutrophilic CRS, with tetracyclines demonstrating better efficacy in patients with eosinophilic CRS.[32] Unfortunately, treatment of CRS with nasal corticosteroids does not seem to improve asthma control.[33] There is increasing evidence that surgical techniques should be tailored to the underlying disease mechanisms, with minimally invasive and mucosa-sparing approaches for patients with localized chronic rhinosinusitis without nasal polyps (CRSsNP) with no or little type 2 inflammation and extended, mucosa-removing approaches for patients with severe type 2 eosinophilic chronic rhinosinusitis with nasal polyps (CRSwNP) with massive B- and T-cell activation, as discussed by Bachert and Akdis.[34] Finally, new innovative treatment approaches, such as humanized mAbs against type 2 inflammatory markers, are currently studied for CRSwNP, and their efficacy is obviously dependent on the inflammatory endotype. With the dawn of biologicals, endotyping of CRS will be inevitable.

A recent cluster analysis primarily based on inflammatory markers revealed 10 clusters, with 4 noneosinophilic clusters partially expressing IL-17, IL-22, IFN-γ, or a combination of these cytokines.[35] When linked secondarily to clinical data, those patients predominantly had CRSsNP and a low prevalence of comorbid asthma. Three clusters showed moderate type 2 inflammation and express IL-5 and possibly IL-22 and interferons; these patients predominantly had CRSwNP and moderately increased asthma comorbidity (<40%). Finally, 3 clusters expressed high concentrations of type 2 cytokines and some of these clusters also expressed IL-17, IL-22, and interferons. Two of those clusters expressed specific IgE antibodies to *Staphylococcus aureus* enterotoxins; these patients had CRSwNP, had a high prevalence of asthma comorbidity of 60% to 70%, and underwent frequent prior surgery (50% to 65%). These results demonstrated that different inflammatory patterns might be found to coexist; however, when type 2 cytokines are expressed, they clearly dominate the inflammation and also affect the course of disease. Most cases of bilateral CRSwNP in the United States and Europe are type 2 biased, and AFRS and AERD show the same inflammatory patterns; about 10% of asthmatic patients with CRSwNP have AERD based on a meta-analysis.[36] Furthermore, there is an association with mucosal presence of bacteria: *S aureus* mucosal presence was recently shown in mast cells,[37] and this was significantly associated with type 2 inflammation in an independent study.[38] The same study also showed that mucosal presence of *Pseudomonas aeruginosa* is associated with expression of TNF-α, interferons, and IL-22.

Recurrence of disease after surgery is of specific interest in patients with CRSwNP because recurrence rates are considerably higher in patients with CRSwNP compared with those with CRSsNP. In a United Kingdom epidemiologic study[39] 57% of patients with CRSwNP or AFRS reported having undergone previous endoscopic nasal polypectomy, of whom 46% reported having undergone 3.3 (range, 2-30) operations. In a Chinese population marked tissue eosinophilia in patients with CRSwNP was associated with the highest recurrence rate compared with other cellular inflammatory cell patterns when patients were followed for at least 24 months postoperatively.[40] In studies from a clinic in Belgium, tissue expression of type 2 cytokines was associated with a higher likelihood of recurrence, whereas tissue expression of interferons reduced this risk.[41] There is emerging evidence that the composition of the nasal microbial community might affect the outcome of surgery as well, with bacterial diversity and relative abundances of Actinobacteria being associated with a better outcome.[42] Thus with the role of type 2 inflammation established, it will be interesting to determine whether the composition of the microbiome is a consequence of the type 2 inflammatory pattern or an independent factor.

The currently available information on biologicals in patients with CRSwNP was recently reviewed.[43] All mAbs studied thus far targeted type 2 inflammatory cytokines, including IL-4, IL-5, and IL-13, or IgE, and all of these studies demonstrated proof of concept in the patients with CRSwNP selected for these studies; more than half of the patients had comorbid asthma, prior surgery, or both. For omalizumab, based on a small number of patients, we discussed that anti-IgE might be efficacious even in nonallergic subjects; this observation was supported by data reflected in a review on omalizumab in patients with atopic and nonatopic asthma.[44] This might open new treatment options also for patients with late-onset nonatopic asthma and those with nasal polyps. In this regard it is reassuring that the results from the EXCELS study suggested that omalizumab therapy is not associated with an increased risk of malignancy.[45] Dupilumab, a biologic drug targeting the IL-4 and IL-13 pathways, was recently studied in a larger proof-of-concept trial and showed superiority to placebo in changes in nasal polyp scores, Lund-Mackay computed tomographic total scores, the 22-item Sino-Nasal Outcome Test, and sense of smell assessed by the University of Pennsylvania Smell Identification Test (UPSIT).[46] Phase 3 trials will now be performed to aim for registration of suitable antibodies for the indication of CRSwNP. Patient-reported outcome measures might play an essential role in tailoring the right intervention to the right patient.[47]

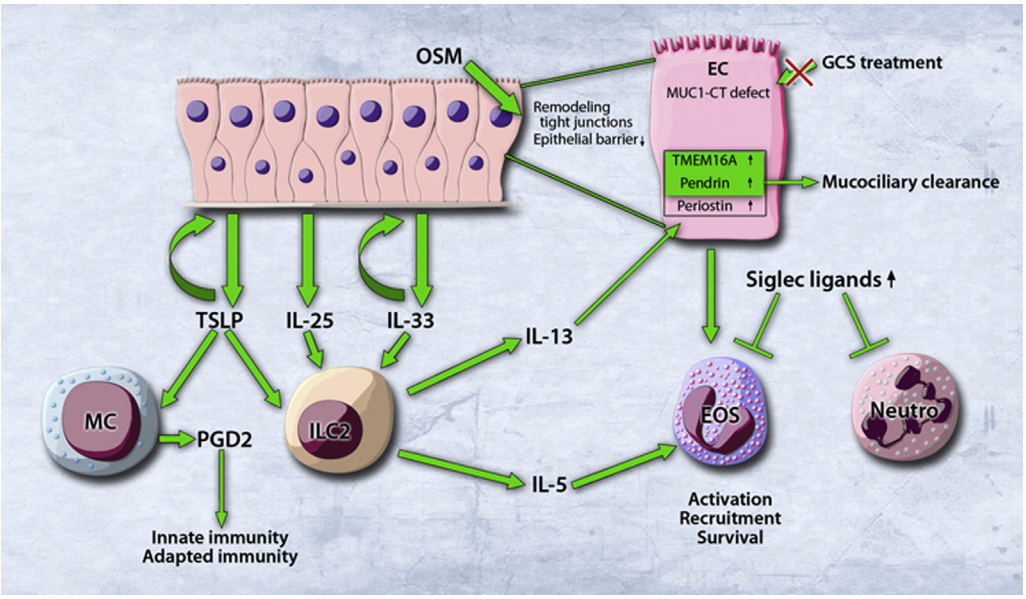

FIG 1. On exposure to allergens or pathogens, TSLP, IL-25, and IL-33 are produced by epithelial cells and directly act on type 2 innate lymphoid cells *(ILC2)*, which in turn produce IL-5 and IL-13. IL-5 acts directly on eosinophils *(EOS)*, whereas IL-13 acts indirectly on eosinophils by promoting the production of periostin in epithelial cells *(EC)*. In addition, IL-13 increases pendrin and TMEM16 production in epithelial cells, which influences mucocilliary clearance. A positive feedback loop between TSLP, IL-33, and their receptors enforces their effect. TSLP can control PGD_2 production in mast cells *(MC)*. OSM acts on epithelial cells by affecting the epithelial barrier and remodeling of tight junctions. A defect in MUC1-CT, which was produced by epithelial cells, can cause failure of glucocorticoid *(GC)* treatment. Siglec ligands are upregulated in disease conditions and have an inhibitory effect on eosinophils and neutrophils *(Neutro)*.

MECHANISMS OF UPPER AIRWAY INFLAMMATION IN PATIENTS WITH CRS

Mucosal inflammation of the upper airways is the result of a complex interaction of diverse mediators produced by a variety of cells (Fig 1). Over the last years, the importance of the mucosal epithelium of the upper airways has been recognized. An overview of factors and their importance to barrier function of the nasal mucosa and pathogenesis of chronic rhinosinusitis was recently reviewed.[48,49] Oncostatin M (OSM) was shown to directly influence this physical barrier because a decreased barrier function and reorganization of tight junction molecules was observed in epithelial cells after OSM stimulation *in vitro*.[50] However, additional knowledge about the cell types producing OSM and their distribution in the tissue would be an asset to determine whether OSM affects the epithelium to the same extent in patients' tissue.

The increased presence of type 2 innate lymphoid cells (ILCs) in patients with CRSwNP and eosinophilia point to a prominent role of innate type 2 reactions in its pathogenesis.[51] Epithelium-derived mediators, such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, are recognized as important mediators of innate type 2 immune reactions. These are typically produced by human airway epithelial cells in response to pathogenic triggers and allergens.[52] Epithelial cells of eosinophilic patients with CRSwNP were shown to have a positive feedback loop between TSLP, IL-33, and their receptors, enforcing the effect.[53] A direct link of IL-25, IL-33, and T_H2 cells in humane disease was shown, suggesting that IL-$17^-RB^+ST2^+$ T_H2 cells are likely to contribute to CRSwNP pathogenesis through the IL-25/IL-33 axis.[54] Also, in Asian patients with CRSwNP, IL-25 overexpression was observed in epithelial and mast cells. Of note, levels of IL-25, which is known to be involved in diverse T_H2-mediated diseases, correlated with factors also involved in T_H1 and T_H17 responses in those patients.[55] The fact that neutralization of IL-25 in a mouse model for nasal polyposis reduced symptoms suggests a central role of IL-25 as a mediator of CRSwNP and represents a possible new target for therapy. However, the necessary confirmation of its role in human subjects is still lacking at this moment. TSLP was shown to control mast cell–derived prostaglandin D_2 (PGD_2) production, which in turn is a major effector of type 2 immune responses. The role of PGD_2 in innate immunity is largely unexplored, although it is well known that innate type 2 immune responses initiated by epithelium-derived cytokines involve both myeloid and lymphoid effector cells that express its receptor, suggesting that PGD_2 plays a role in this system. In patients with CRSwNP and AERD, increased urinary levels of the stable PGD_2 metabolite were found, suggesting that a dysregulation of this system contributes to the pathophysiology of AERD.[56]

A new role for the cytoplasmic tail of mucin 1 (MUC1-CT) expressed by epithelial cells was proposed in the modulation of the anti-inflammatory effects of corticosteroids in patients with CRSwNP. Experiments revealed formation of a protein complex between MUC1-CT and the glucocorticoid receptor (GR) α, which protected against GR phosphorylation induced by Toll-like receptor agonists and helped GRα to translocate into the nucleus to exert its anti-inflammatory effects. These findings could serve as an explanation for the observation that corticosteroids cannot repress inflammation in individual patients with CRSwNP because the MUC1-CT–GRα complex is deficient. However, a

limitation of this work is the lack of proof in primary epithelial cells,[57] and further work is needed.

The involvement of periostin in T_H2-driven pathologies, including asthma, was shown in recent years. Periostin expression was found to be enhanced in patients with CRSwNP and likely to be associated with eosinophil localization. Because periostin and IL-25 expression were linked to one another in other pathologies, this could be an interesting pathway in the context of CRSwNP pathology. The exact role of periostin in patients with CRSwNP is still unclear, but integrin expression on eosinophils and overexpression of ECM are likely to be involved in this process.[58,59] Periostin and pendrin levels were found to be correlated with IL-13 levels, suggesting possible induction by this cytokine. The induction of pendrin, an apically expressed ion exchanger, could in turn modulate mucin 5AC expression and thus affect the mucocilliary clearance of pathogens.[59] Another epithelial transmembrane transporter protein, TMEM16A, was also found to be induced by IL-13 and to regulate mucin 5AC expression.[60] However, it is likely that expression of both pendrin and TMEM16A is affected by more T_H2 cytokines than just IL-13.

Eosinophils, as part of both the innate and adapted immune systems, gain appreciation as defense cells and for their contribution to airway pathologies through thus far undiscovered mechanisms.[61] Histone H_1-bearing DNA traps were found in eosinophilic secretions from patients with CRSwNP. Those traps were shown to entrap bacteria and fungi *in vitro*, suggesting a role in mucosal defense at multiple levels for eosinophils. Sialic acid–binding protein (Siglec) 8 on eosinophils and Siglec-9 on neutrophils engage sialoglycan ligands on airways to control and diminish ongoing inflammation. In the case of CRS, Siglec-8 and Siglec-9 ligand expression was enhanced but apparently did not prevent disease.[62] The upregulation of Siglec-9 ligands is regulated through the nuclear factor kB pathway and results in their enhanced expression on MUC5B. However, the extent (if any) to which it moderates disease is currently unknown, and much remains to be discovered about Siglec ligands and their expression in human tissues.

The role of *S aureus* and its immune proteome is a well-recognized and intensively investigated topic. Interestingly, staphylococcal protein A was suggested to have both inflammatory and regulatory effects in the pathogenesis of CRSwNP. Coupling of staphylococcal protein A to immunoglobulins by using IgG or autologous serum strongly and broadly inhibited enterotoxin-induced T_H1, T_H2, and T_H17 inflammatory cytokine production.[63] Whether this inhibition can induce improved bacterial survival by IL-10 induction should be investigated further.

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