

Clinical Commentary Review

The Development of the Mucosal Concept in Chronic Rhinosinusitis and Its Clinical Implications

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In the last 2 decades, an increasing understanding of pathophysiological mechanisms in chronic rhinosinusitis (CRS) opened an avenue from phenotyping to endotyping, from eosinophilic inflammation to type 2 immunity, and from the ventilation and drainage paradigm to the mucosal concept for therapeutic considerations. With the advent of type 2 endotyping and targeted biomarkers, precise endotype-driven therapeutic options are possible including biologics and adapted surgical approaches. We here aim to focus on the complexity and heterogeneity of the features of CRS endotypes, especially for those with nasal polyps, including its history, latest developments, clinical associations, and endotype-driven solutions. In order to better manage uncontrolled severe CRS in clinical practice, medical decisions based on a profound understanding of the pathology and immunology of this heterogeneous disease, aiding a precision-medicine based approach for patient's treatment, are pivotal. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;■:■-■)

Key words: Chronic rhinosinusitis; Nasal polyps; Endotype; Type 2 inflammation

Chronic rhinosinusitis (CRS) is a common inflammatory disease characterized by the presence of 2 or more symptoms including nasal congestion, nasal discharge, facial pain, or headache, and loss of smell for more than 12 weeks. Supportive

objective evidence is either endoscopic findings or computed tomography scan. Clinically, it is usually divided into 2 phenotypes, CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) based on nasal endoscopic findings. Patients with CRSwNP tend to experience more severe clinical symptoms, higher postoperative recurrence rates, and more asthma comorbidity than patients without nasal polyps (NPs).¹

Over the past 20 years, especially in the last decade, attempts have been made to introduce endotypes within the phenotypes of CRS, especially for severe disease. In 2013, an international Practical Allergy (PRACTALL) document clarified that defining a CRS phenotype merely based on clinical observations was insufficient because it did not provide comprehensive insight into its underlying cellular and molecular pathophysiological mechanism. The introduction of endotypes, for example, based on pathophysiological characteristics, might provide a better understanding of the heterogeneous nature of CRS² and support diagnosis and treatment.³ This review focuses on the complexity and heterogeneity of the features of CRS endotypes, including tracing back to its history, clinical associations, and latest developments with endotype-driven solutions. This discussion highlights not only the developmental path over recent years, from a cellular trait to molecular features, from physical principles such as ventilation and drainage to the importance of mucosal inflammation in the mucosal concept, from clinical phenotypes to biomechanical endotypes, from the pharmacological standard of care to biologics, from functional endoscopic sinus surgery to a variety of approaches, but also endotype-driven medical algorithms that could be applied in daily clinical practice.

THE DEVELOPMENT OF ENDOTYPING IN CRS From physical condition to heterogeneous disease

Back in the 1980s, rhinologists considered sinusitis as a physical condition owing to secretion retention and poor ventilation, with consequent infection of adjacent sinuses and ciliary activity impairment; they also deemed that NPs originated from areas of intense mucosal contact, causing considerable pressure on the mucosa leading to discomfort.⁴ Forerunners such as Messerklinger, Stammberger, Wigand, and Kennedy advocated and popularized novel endoscopic surgical approaches into clinical practice with considerable efficacy throughout the world. The concept of functional endoscopic sinus surgery aiming to reestablish sinus drainage and ventilation through the natural ostia was born.⁵ It was Messerklinger who first proposed and emphasized the importance of functional surgery, which further popularized the English-speaking world by his successor Heinz Stammberger and U.S. colleague David Kennedy building upon his ideas. During the same period of time, people recognized the

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This work was supported by the China Scholarship Council (202008110300).

Conflicts of interest: C. Bachert is an Advisory Board member and speaker for Novartis, GSK, Astra-Zeneca, Sanofi, ALK, and Mylan. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication April 27, 2021; revised manuscript received and accepted for publication October 25, 2021.

Available online ■■

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2213-2198

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<https://doi.org/10.1016/j.jaip.2021.10.054>

Abbreviations used

CRS- Chronic rhinosinusitis
 CRSsNP- Chronic rhinosinusitis without nasal polyps
 CRSwNP- Chronic rhinosinusitis with nasal polyps
 ECP- Eosinophil cationic protein
 IgE- Immunoglobulin E
 IFN- γ -Interferon-gamma
 IL- Interleukin
 ILC2s- Type 2 innate lymphoid cells
 M2- Macrophage
 N-ERD- Nonsteroidal anti-inflammatory drug-exacerbated respiratory disease
 NP- Nasal polyp
 Th- T helper
 TSLP- Thymic stromal lymphopoietin

coexistence of rhinitis and sinusitis with the close physiological and pathophysiological association; thus, the term rhinosinusitis was then introduced and later widely accepted by international scholars. The Messerklinger technique had a wide range of indications but excluded nasal polyposis.⁵ In his experience, patients with diffuse nasal polyposis suffered from a high recurrence rate, and this condition was considered a general mucosal disease not fully understood at that time⁵ rather than a sinus disease. Later, being curious about its underlying mechanisms, in the first decade of the 21st century, researchers aimed to understand the pathological and immunological mechanisms, unveiling the potential of pathoimmunological elements in CRS such as eosinophils, neutrophils, leukotrienes, and other cells and mediators. Thanks to the understanding of inflammatory mechanisms, CRS began to be accounted as a heterogeneous disease, although it was still not clear why NPs would occur.⁶⁻⁸

From eosinophilic inflammation to T helper 2 inflammation

Eosinophil. The first attempt to quest the underlying pathophysiological mechanism of CRS was to explore the histopathological pattern in sinonasal mucosa. Eosinophils, which were first discovered and identified in the blood by German scientist Paul Ehrlich in 1879, is a lineage of granulocyte that develop during hemopoiesis in bone marrow responsible for combating parasites and inflammation in the human body.⁹ For years, scientists strived to figure out the mechanism of eosinophil activation, recruitment, retention, and survival within certain tissues in different diseases, exploring effector functions, granule protein (major basic protein, eosinophil cationic protein [ECP], Charcot-Leyden crystal protein [galectin 10]), and lipid mediators (such as leukotriene C₄, 5-hydroxyicosatetraenoic acid, arachidonate 15-lipoxygenase, and platelet-activating factor). In 1973, Kaliner et al were the first to demonstrate that NP tissue released leukotrienes and histamine, regardless of the atopic status.⁷ In 1988, rhinologists first identified tissue hypereosinophilia in CRS and found it associated with a higher likelihood of extensive CRS.⁶ Newman and colleagues¹⁰ first reported a case series of 104 patients with CRS whose severity was assessed by computed tomography scans correlating well with eosinophilia; approximately 65% of patients with extensive CRS showed tissue or serum eosinophilia, whereas eosinophilia was present in less than 10% of CRS patients with less extensive disease. Subsequently, studies confirmed that patients with extensive CRS indeed

widely demonstrated eosinophilia regardless of their atopic status.^{11,12} Two distinctive histological patterns were found in CRS, eosinophilia-dominated CRS with NPs and CRS characterized by glandular hyperplasia and hypertrophy without NPs,¹³ indicating that CRSwNP should be considered a distinct disease entity from CRSsNP. Later studies further supported the concept that CRSwNP and CRSsNP were indeed 2 different disease entities in many aspects (Table I).¹⁴⁻¹⁶ The inflammatory infiltration in NPs included a mixture of eosinophils, neutrophils, lymphocytes, and plasma cells.¹⁷ Nasal polyposis was characterized by an eosinophilic inflammation, which appeared even in the early formation of nasal polyposis¹⁸; this inflammation was closely associated with higher recurrence rates and less postoperative improvement in symptoms and quality of life.¹⁹⁻²¹ Of interest, CRSwNP patients from southern China did not show a similar eosinophilic pattern as the white population from the previously discussed studies because they were more neutrophilic and lacked the typical increase in eosinophilic indicators.^{22,23} As a result, evidence supporting a variety of inflammatory phenotypes was accumulating and, therefore, unmet needs toward understanding endotypes were obvious.

In the last 2 decades, the percentage and absolute counts of eosinophils in CRS are increasing not only in Asian countries,²⁴ although ethnic and geographical differences are still major differentiators. Second-generation U.S. Asian patients with CRSwNP were found to be significantly less eosinophilic and showed lower levels of ECP, a marker of eosinophil activation, than the Caucasian population,²⁵ similar to native Asian patients. However, no consensus has yet to be found for the criteria of eosinophilic CRS in the international scientific community, and current cut-off criteria vary from 5 to as high as 350 eosinophils per high power field.²⁶

Indeed, eosinophils were considered cardinal effectors in the classical type 2 inflammation. Elevation of blood eosinophils (>150 cells/ μ L) and sputum eosinophils (>2%) were proposed to define type 2 inflammation.²⁷ Similarly, peripheral eosinophil levels of more than 150 cells/ μ L, together with high serum immunoglobulin E (IgE) and comorbidity of asthma or nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) was also proposed as a strong indicator of type 2 CRSwNP.²⁸ However, the count might vary with different biopsy locations.²⁹ Notably, the status of eosinophilia is easily affected by drugs; oral corticosteroid treatment could significantly downregulate the level of peripheral eosinophils,³⁰ and even local nasal corticosteroids could dramatically decrease the level of tissue eosinophil percentages but not affect the level of inflammatory mediators (interleukin -5 [IL-5], ECP, albumin) and subsets of T cells (T helper 1 [Th1], Th2, Th17, Treg cells),³¹ indicating type 2 inflammation still persists in the circumstances.

TABLE I. Major immunological distinctions between CRSwNP and CRSsNP at the beginning of the 21st century

	CRSwNP	CRSsNP
Inflammatory mediators ²⁸	IL-5 and ECP $\uparrow$	INF- γ $\uparrow$
Tissue remodeling ¹⁶	MMP-7 $\uparrow$	MMP-9 and TIMPs $\uparrow$
Prominent inflammation ¹⁴	Eosinophilic	Neutrophilic

MMP, Matrix metalloproteinase; TIMPs, tissue inhibition of metalloproteinases.

Chemokines and cytokines. At the same time, because a large proportion of NPs were associated with prominent eosinophilic inflammation, scientists sought to explore what is beneath eosinophilic inflammation and elaborated insights on the possible regulation of eosinophil proliferation, migration, activation, and survival through measuring chemokines and activators such as IL-5, eotaxin, and regulated upon activation, normal T cell expressed and presumably secreted.¹⁸ The current concept and mechanism of eosinophilic inflammation were originally elaborated by immunologists and then were gradually applied to CRS. For instance, IL-5 is the cardinal cytokine in eosinophils' life span, promoting the activation, proliferation, development, and survival of eosinophils cooperating with other β common chain cytokines such as IL-3 and granulocyte-macrophage colony-stimulating factor.⁹ In the bone marrow, it stimulates the growth and differentiation of eosinophil lineage; it promotes the release of eosinophil granular proteins; in the peripheral tissue compartment, IL-5 induces eosinophilic accumulation by upregulating its adhesion; for activated mature eosinophils, IL-5 inhibits eosinophilic apoptosis.⁹ Both IL-5 and its receptor, the secreted form of IL-5R α rather than the membrane-anchored isoform, were found upregulated in NPs.^{32,33} Further study revealed that high levels of Charcot-Leyden crystals in type 2 CRSwNP remained after eosinophilic extracellular traps and then promoted neutrophilic inflammation toward neutrophilic extracellular trap cell death eventually, suggesting a complex regulatory network³⁴ contributing to persistent disease.

T-cell subsets. T-cell subsets were also widely introduced and studied in mice and human models of airway diseases during this time period.^{22,35-38} Upon stimulation of dendritic cells, T cells are activated to differentiate and stimulate immune responses; Th cell subsets direct immune responses and promote controlling pathogens by producing signature cytokines: Th1 cells express tumor necrosis factor (TNF) and interferon-gamma (IFN- γ), Th2 cells express IL-4, IL-5, and IL-13, Th17 cells produce IL-17.³⁹ As 2 main regulators of Th1/Th2 differentiation, T-bet induces differentiation along the Th1 pathway, and GATA-3 enhances Th2 cytokine production and polarization.²² Van Zele et al⁴⁰ reported that the Th1/Th2 ratio (calculated by IFN- γ /IL-5 ratio) characterized CRSsNP as a Th1 polarized disease whereas CRSwNP showed Th2 polarization with eosinophilic inflammation and hyper-IgE expression. As a matter of fact, asthma, also characterized by eosinophilic inflammation, was the first airway disease to be explored with respect to the immune responses, and much was learned from translating this research to CRS. After decades of experiments carried out in animal models, a seminal work in human asthma by means of airway epithelial brushings from asthmatic patients and healthy controls identified 2 distinct subgroups based on the extent of Th2 inflammation, which was in accordance with previous results in mice models.³⁶ Subsequently, cluster analysis, an unbiased statistical method, was for the first time used to study the inflammatory endotypes in CRS in 2016.⁴¹ This study demonstrated that clinical traits such as asthma comorbidity as well as postoperative recurrence were related to increased expression of ECP, IL-5, IgE, and *Staphylococcus aureus* enterotoxin-specific IgE, markers of Th2-biased inflammation, whereas within the non-Th2 group, inflammation was more multidimensional, involving Th1, Th17, and Th22.^{41,42} For NPs from southern China, as mentioned previously, a mixed Th1/Th17

inflammatory pattern was observed, accompanied by a decrease in the Th2 transcription factor GATA-3, but an increase in ROR- γ and IL-17.²² Recently, the heterogeneity of the airway inflammation within CRSsNP was also demonstrated; among 240 CRSsNP patients, 49% expressed upregulated IL-4, IL-5, ECP, and IgE together with a lower IL-17, associated with higher asthma comorbidity and recurrence rates, showing a similar but less severe type 2 immune response compared with CRSwNP.⁴³ Thus, both CRSwNP and CRSsNP do show type 2 and non-type 2 inflammatory reactions, which differ in distribution and severity.

From Th2 inflammation to type 2 inflammation

In recent years, with the development of endotypes, a comprehensive body of knowledge was built up on cells and mediators relevant in CRS, primarily based on findings established in basic immunology and finally asthma. Initially, as mentioned previously, Th2 cells were considered to be the primary source of the inflammatory cytokines and early studies supported this theory. However, studies in mice models indicated the existence of another cytokine source apart from Th2 cells, including invariant T cells, Th1, eosinophil/basophil progenitor cells, and type 2 innate lymphoid cells (ILC-2s).⁴⁴⁻⁴⁶

Epithelial cells. It was recognized that, as the first line of defense of innate immunity against external stimuli including pathogens, chemicals, and antigens, epithelial cells were already important sensors capable of producing a wide range of Th2-promoting cytokines, also called the alarmins, such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP).⁴⁷⁻⁴⁹ A recent study that used single-cell sequencing technique demonstrated that the reduced epithelial cell diversity might play a role in type 2 inflammation of CRSwNP and the secretory cells were characterized by several genes such as *ALOX15*, cystatin SN, *SERPINB3*, and periostin.⁵⁰ Cystatin SN and *ALOX15* were later confirmed to be essential in type 2 NPs.^{51,52}

Other Th2-cytokine producers. Further, several landmark publications using mouse helminth infection models identified a group of potent lineage-negative Th2-cytokine producing cells distinct from T and B cell, ILC-2s, which now widely are accepted as substantial Th2 cytokine producers.⁵³⁻⁵⁶ Later, the expression and activity of TSLP were found to increase significantly in CRS,⁵⁷ which might promote CD4⁺ T cells differentiating into Th2 cells.⁵⁸ In addition, TSLP could induce Th2 inflammation by activating ILC-2 to overproduce Th2-cytokines (IL-4, IL-5, and IL-13).⁵⁹ In addition, IL-33 was found to be positively correlated with Th1/17 inflammation as well as local neutrophil recruitment in CRSwNP.⁶⁰ Further, macrophages were also found to represent a potential player in type 2 inflammation, with the concept of alternative activation macrophage (M2) induced by Th2 cytokines IL-4 and IL-13 being introduced by immunologists.^{61,62} In mouse bacterial infection models and IL-21R-deficient mice, it was found that IL-21 accentuated M2-induced type 2 inflammation by upregulating IL-4R α and IL-13R α .⁶³ In human and mouse lung macrophages, the IL-33/ST2 pathway could amplify M2 polarization in an IL-13-dependent manner and contribute prominently to airway inflammation.^{64,65} In addition, IL-33 signaling was also essential for the development of remodeling by alternative activation of macrophages in murine lungs.^{66,67} We and others also demonstrated IL-21 to be increased in NPs, associated with

disease severity.^{68,69} Moreover, the IL-33/ST2 pathway was found to be the critical pathway for *S. aureus* and its bacterial allergen.^{70,71} Alternatively activated M2 macrophages are more prevalent in CRSwNP than in CRSsNP, which is also positively correlated with upregulated IL-5, ECP and IgE as well as downregulated IFN- γ .⁷² Nevertheless, the mechanism of tissue remodeling and the role of macrophages in type 2 inflammation are still unclear and future studies are urgently needed.

B cells and local immunoglobulin. Originally, B cells were thought to be pivotal in type 2 inflammation because of the upregulated local IgE synthesis. As a matter of fact, besides IgE, other subtypes of immunoglobulins (IgG, IgA, and IgM) were also significantly upregulated locally in NPs.⁷³ This overproduction of IgM, IgG1, IgG2, IgG4, IgA, and IgE in NP tissues can be predominantly found in patients with type 2 inflammation. Interestingly, local IgE in NPs appears to be polyclonal and functional, contributing to the continuous chronic inflammation via mast cell activation.⁷⁴ Further, a high level of B-cell activation and class switching was found in NP tissues, either via the classical sequential way or via direct switching.^{75,76} *Staphylococcus aureus* enterotoxins in NP upregulate local IgG and IgE, indicating its role was not limited to the upregulation of local IgE.⁷³ Although superantigens may explain the high levels of local immunoglobulins in NPs in a typical type 2 inflammation, it also can be observed in some patients without *S. aureus* colonization.

Further, the organization of secondary or ectopic lymphoid tissues was described in NP tissues,^{77,78} with B cell-activating factor⁷⁹ and CXCL13⁸⁰ levels being upregulated. However, to date, the underlying regulatory mechanism on local immunoglobulin hyperproduction and upstream drivers, as well as importantly the polyclonality of local immunoglobulin in NP tissues, are still poorly understood.

Microbiome. The dysbiosis of bacterial community composition and less richness or diversity are also contributing to the pathogenesis and development of CRS.^{81,82} However, a recent study reported differential bacterial composition at the genus level between control and CRSwNP, but no significant differences between these 2 groups in sinus bacterial diversity.⁸³ Another large multicenter study identified that the most abundant genera in human nasal sinus with or without CRS were (1) *Corynebacterium* and *Staphylococcus* (the most abundant), (2) *Streptococcus*, *Hemophilus*, and *Moraxella* (the most abundant cocolonizers).⁸⁴ Reduction of *Corynebacterium* in CRSwNP might allow *S. aureus* to switch from commensalism to virulence.⁸⁴ Conversely, *Corynebacterium* was enriched in CRSsNP and the presence of *Corynebacterium*-dominant community was associated with elevated IL-5 expression.⁸⁵ Thus, the balance of the germs is of utmost importance.

The nomenclature for asthma first evolved from the original Th2 inflammation concept toward type 2 inflammation, including several immune cells (Figure 1) and associated type 2 cytokines to regulate relevant immune responses such as epithelial cell activation; mucus secretion; CD4⁺ T cell activation; B cell differentiation and immunoglobulin production; eosinophil mobilization, activation, and survival; macrophage activation; and finally, airway remodeling.⁴⁶ Later, the terminology was also appreciated for the upper airways.⁸⁶ Today, the type 2 and non-type 2 inflammation differentiation (including

types 1 and 3) is used for inflammatory endotypes because the importance of such differentiation for asthma comorbidity and risk of recurrence have been recognized.⁴¹ An increasing shift toward the type 2 endotype of CRS has been reported not only in Asia but also in the European population, proven by long-term follow-up studies.^{84,87}

How to identify type 2 inflammation in CRSwNP

Recently, the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) developed a consensus on the definition and practical algorithms of uncontrolled severe, type 2 inflammation of CRSwNP, as well as the indication for biologics.⁸⁸ As mentioned previously, this approach was initially originated in a cluster analysis, which was later further supported by another group in the U.S. population.⁸⁹ Similarly, asthma is viewed as an umbrella term for varying endotypes and phenotypes,⁹⁰ and an endotyping approach based on type 2 inflammation has been introduced. Besides asthma, other type 2 diseases, such as N-ERD, atopic dermatitis, allergic rhinitis, urticaria, food allergy, and eosinophilic esophagitis are closely associated with CRSwNP and increase the likelihood of type 2 inflammation in the upper airways. Apart from comorbidities, biomarkers like blood eosinophils of greater than 300 cells/ μ L and a total serum IgE of greater than 150 kU/L represent strong indicators for type 2 CRSwNP, but algorithms for clinical use have to be defined per population.

Apart from nasal tissue, nasal lavage fluid, nasal secretions, nasal swab/scraping and peripheral blood could be used to identify endotypic biomarkers. A most recent study suggested that CXCL9 and CXCL10, ECP, and CCL26, together with colony-stimulating factor 3 in nasal lavage fluid could be biomarkers to help distinguish tissue endotypes of CRSsNP.⁹¹

Defining the severity of type 2 inflammation is also important. According to the endotypes of CRS based on unsupervised cluster analysis, 3 endotypes including non-type 2, moderate type 2, and severe type 2 were defined,⁴¹ based on cytokines and mediator concentrations. The latter was characterized by highest recurrence risk, higher local IgE, and expression of *Staphylococcus aureus* enterotoxin specific IgE. Moderate type 2 had 10% to 40% asthma risk, and the severe group had 40% to 70% risks.

CONSEQUENCES FOR THE CLINIC: ENDOTYPE-DRIVEN DECISIONS

Endotype-driven clinical decisions are the only way toward precision medicine for treating CRS. A number of studies have shown the high recurrence and reoperation rates in type 2 CRS, especially for those uncontrolled severe CRSwNP patients.^{1,92-103} What is more, for patients with other severe type 2 comorbid diseases such as late-onset asthma, endotype-driven biologics could be a valuable alternative to surgery because they can control both local and systemic symptoms and reduce systemic corticosteroid use and sinonasal surgery rate.¹⁰⁴

Surgical approaches

From the 1970s until recently, the main concept of surgical treatment of CRS remained functional mucosa-sparing surgery, reestablishing sinus drainage and ventilation through the natural ostia. Thus, CRSwNP was treated in an identical approach as CRSsNP, although it was already clear that the approach for NPs was not providing long-lasting results. The list of publications reporting NP recurrence is long.^{1,92-103} Recurrence rates ranged

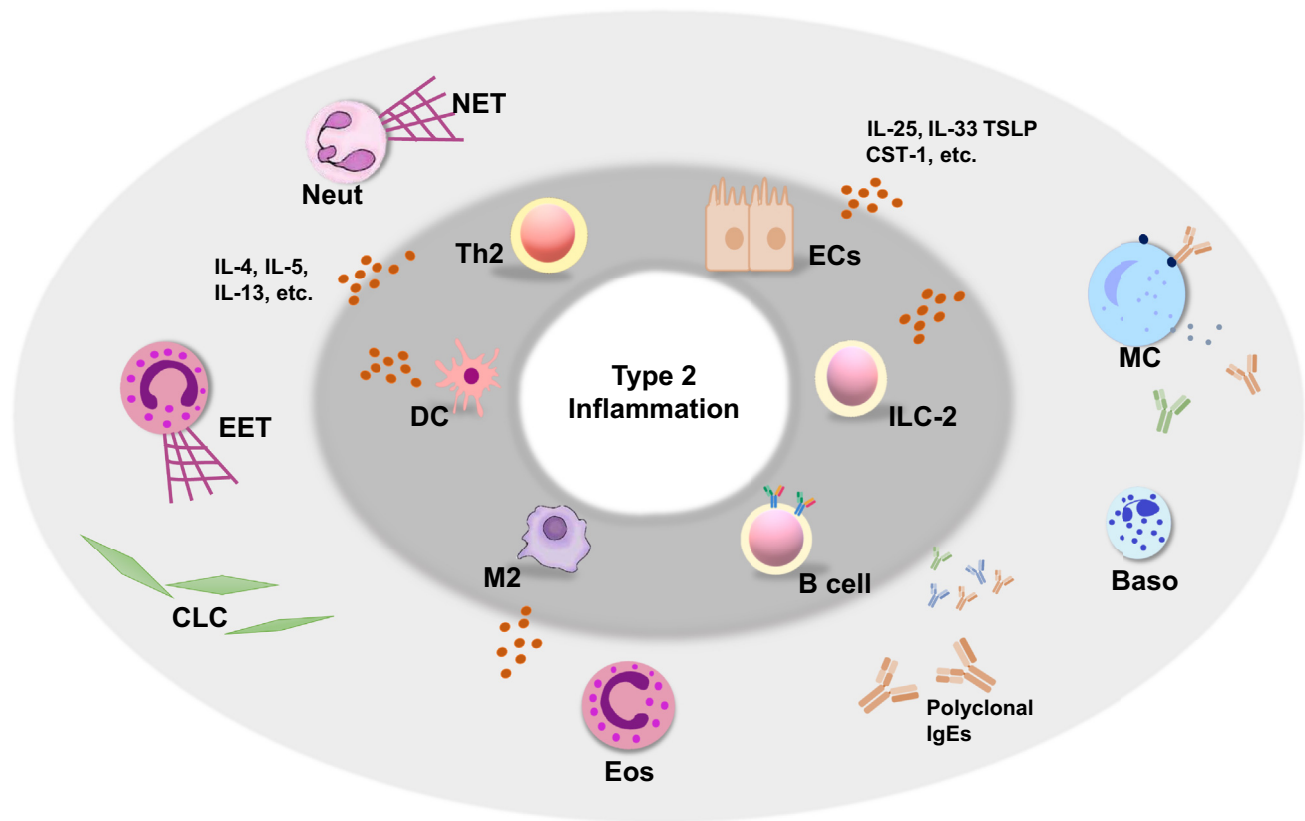


FIGURE 1. Participants in type 2 inflammation in CRSwNP. Multiple cells participate in type 2 inflammation of CRSwNP. The inner circle indicates major promoter cells including Th2 cells, epithelial cells (ECs), ILC-2, B cells, M2, and dendritic cells (DCs). The outer circle indicates downstream effector cells and molecules. *Baso*, Basophil; *CST-1*, cystatin SN; *EETs*, extracellular eosinophilic traps; *Eos*, eosinophils; *MC*, mast cell; *NETs*, neutrophilic extracellular traps; *Neut*, neutrophil.

from 13.4% to 78.9% and are strongly dependent on the time frame of observation (Table II^{1,92-103}). However, as discussed previously, type 2 NPs representing 85% of the cases are prone to recur whereas non-type 2 NPs do not; also for CRSwNP, such differentiation has been shown, with a moderate type 2 inflammation present in about 50% of cases.⁴³ Therefore, specifically in CRSwNP, endotype-driven surgical approaches should be

adapted, taking into account the mucosal inflammation, the high likelihood of recurrence, the likely long-term duration of disease, and the disturbed mucosal healing under type 2 inflammatory conditions. For non-type 2 and moderate type 2 CRSwNP, the surgical procedure may still consist of opening up all sinuses (full house), removing all polyps but preserving sinus mucosa, and applying topical corticosteroids after surgery, in the United States

TABLE II. Long-term postoperative recurrence rates of CRSwNP after endoscopic sinus surgery as reported in the literature

First author	Year	Patient number	Study design	Follow-up (mo)	NPs recurrence rate (%)
Nakayama ⁹²	2011	175	Prospective	17.5	22.9
Ikeda ⁹³	2013	130	Prospective	48	36.2
Vlaminck ¹⁰²	2014	221	Prospective	36	39.6
Brescia ⁹⁸	2016	179	Prospective	18–47	13.4
Grgić ⁹⁵	2015	30	Prospective	24	36.7
Lou ⁹⁶	2015	387	Retrospective	29–39	55.3
Tokunaga ⁹⁷	2015	1,716	Retrospective	22.6	23.1
Brescia ⁹⁴	2015	143	Prospective	9–29	14.7
DeConde ¹	2017	129	Prospective	18	40
Veloso-Teles ¹⁰⁰	2017	85	Retrospective	9–108	31
Calus ⁹⁹	2019	47	Prospective	148	78.9
Saratziotis ¹⁰¹	2021	150	Prospective	12	21.7
Vlaminck ¹⁰³	2021	133	Prospective	120	62

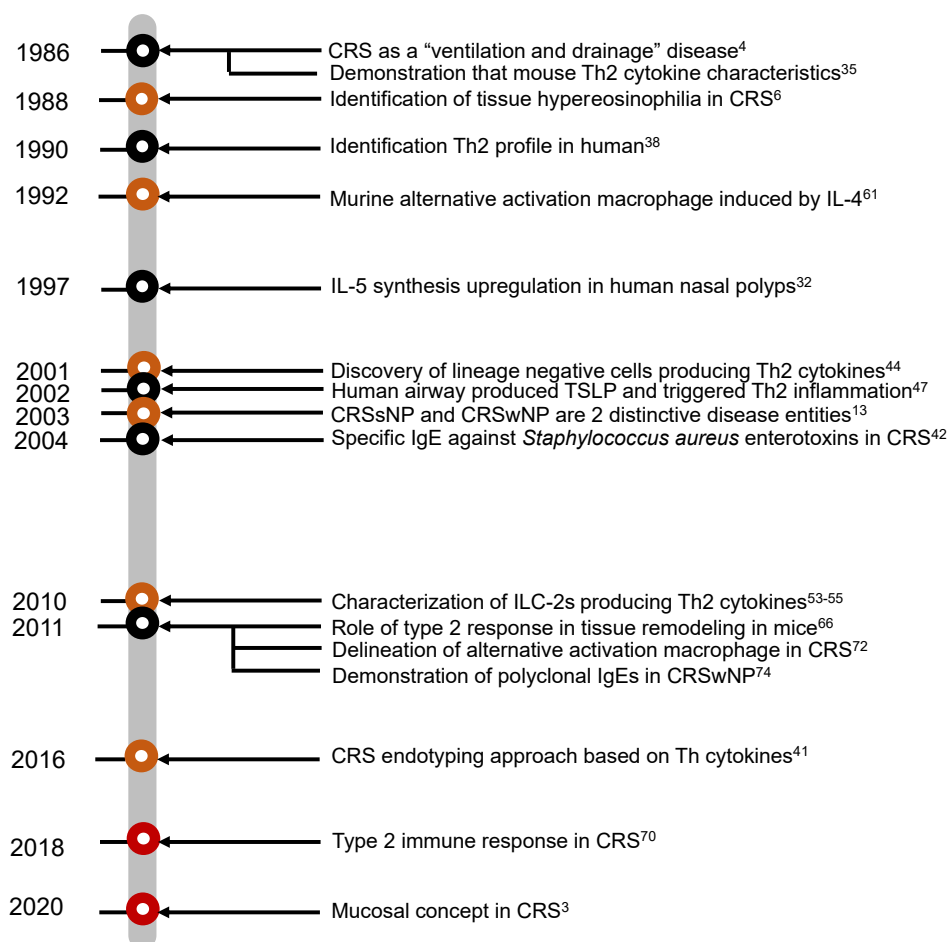


FIGURE 2. A timeline of important discoveries in inflammation of airway mucosa and conceptual developments in CRS. Since the characterization of Th2 cytokine profile in mice,³⁵ a number of important discoveries have continuously expanded our view on type 2 inflammation in humans. The concept of CRS has now shifted from a physical ventilation and drainage paradigm to the mucosal concept.

also as coated implants.^{105,106} However, a prospective study showed that, with endoscopic sinus surgery and continuous medical treatment, there were still 40% patients experiencing polyp recurrences over 18 months.¹ Recently, a novel approach of completely removing both polyps and the diseased sinus mucosa (reboot approach) from the sinuses was, therefore, proposed with a lower recurrence rate and better improvement in symptoms and quality of life.¹⁰⁷ Such a complete removal of sinus mucosa was following a study that demonstrated that the inflammation in type 2 severe CRSwNP was not limited to NPs but widely expressed also in the nonpolypoid sinus mucosa of all sinuses, with similarly high levels of IgE, ECP, and IL-5.¹⁰⁸ Reboot surgery in severe type 2 CRSwNP should be performed by experienced surgeons.

Although about two-thirds of patients with biologics did not need surgical procedures,¹⁰⁹ surgery may also be performed under treatment with biologics for type 2 immune disease, if patients responded to the biologic and still suffered from uncontrolled symptoms. According to recent data from our clinic, sinus surgery during the course of a biologic is safe, and postoperative wound healing is undisturbed (publication pending).

Biologic treatment and available biomarkers

Several biologics targeting type 2 inflammation (anti-IL4R α [dupilumab], anti-IL5 [reslizumab, mepolizumab], anti-IL5R [benralizumab], and anti-IgE [omalizumab]) have been developed and partially already proven efficacy in phase 3 clinical trials¹⁰⁹ (dupilumab [NCT 02912468 and NCT02898454] and omalizumab [NCT03280550 and NCT03280537]). Significant improvements in polyp size, nasal symptoms, and smell impairment as well as the quality of life among other parameters were observed.^{109,110} These novel treatments for uncontrolled severe CRSwNP may be used alone or in combination with surgery as discussed.⁷¹

In clinical practice, it is essential to identify patients who might benefit from biologics. Currently, identification of patients with type 2 CRSwNP could rely on both clinical traits such as comorbid late-onset asthma or N-ERD and biomarkers (blood eosinophils, high level of serum total IgE and serum *S. aureus*-endotoxin-IgE positivity).²⁸ Clinical traits and biomarkers will be helpful to select severe patients with type 2 immune reactions, uncontrolled by the current standard of care, and may in the future predict response to specific biologic treatment; currently, no such markers have been identified.

DISCUSSION

With the advent of endotyping and the concept of mucosal inflammation (Figure 2), multiple type 2—targeting biologics and adapted surgical approaches are available on the way to precision medicine for CRS patients. In the near future, we will eventually gain more insight into the optimal clinical patient selection, drug selection, appropriate duration of treatment, evaluation of responsiveness, continue or stop rules, and the optimal care pathways also including adapted surgical interventions for severe type 2 CRSwNP patients.

However, there are still unmet needs to current knowledge of the disease. Although we realize the importance of type 2 inflammation, we do not understand its initiation. Potential type 2 drivers maintaining the disease even after treatment, and reliable biomarkers for optimizing the selection of patients for biologic treatments need to be more elucidated. Apart from inflammation, which has been widely studied, mechanisms such as remodeling need to be further clarified.

Yet no non—type 2 targeted biologics have been registered, and biologics have just entered in trials for CRSsNP. Surgical concepts for type 2 CRSwNP patients, and also the relatively small CRSsNP population, need to be further developed and confirmed in appropriate clinical trials. This process needs to be accompanied by the search for adequate biomarkers. However, it is clear that the recent achievements undoubtedly shift our understanding from a physical ventilation and drainage paradigm to the mucosal concept because it has been clearly demonstrated that chronic sinusitis is a mucosal disease. Type 2 immune reactions are the key to understand the clinical prognosis and severity of the disease. The concept of adapted surgical approaches and targeted type 2 biologics as innovative treatment options, often in combination, will change our care pathways profoundly and offer the currently uncontrolled severe CRSwNP patients so far unexperienced progress.

Acknowledgments

C. Bachert, N. Zhang, and L. Zhang contributed to the scientific concept of the review. N. Zhang and Y. Huang conceived the article structure, wrote the article, and searched the literature. All these authors read, revised, and approved the final manuscript.

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