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Immunopathogenesis of Chronic Rhinosinusitis and Nasal Polyposis

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acantholysis, acanthosis, allergy, chronic rhinosinusitis, eosinophilic inflammation, epithelial barrier, epithelial-to-mesenchymal transition (EMT), glandular hyperplasia, nasal polyp, sinus disease

Abstract

Chronic rhinosinusitis (CRS) is a troublesome, chronic inflammatory disease that affects over 10% of the adult population, causing decreased quality of life, lost productivity, and lost time at work and leading to more than a million surgical interventions annually worldwide. The nose, paranasal sinuses, and associated lymphoid tissues play important roles in homeostasis and immunity, and CRS significantly impairs these normal functions. Pathogenic mechanisms of CRS have recently become the focus of intense investigations worldwide, and significant progress has been made. The two main forms of CRS that have been long recognized, with and without nasal polyps, are each now known to be heterogeneous, based on underlying mechanism, geographical location, and race. Loss of the immune barrier, including increased permeability of mucosal epithelium and reduced production of important antimicrobial substances and responses, is a common feature of many forms of CRS. One form of CRS with polyps found worldwide is driven by the cytokines IL-5 and IL-13 coming from Th2 cells, type 2 innate lymphoid cells, and probably mast cells. Type 2 cytokines activate inflammatory cells that are implicated in the pathogenic mechanism, including mast cells, basophils, and eosinophils. New classes of biological drugs that block the production or action of these cytokines are making important inroads toward new treatment paradigms in polypoid CRS.

anosmia:

loss of the sense of smell

polyp: an abnormal growth of tissue in the sinuses and nose

CRSwNP: chronic rhinosinusitis with nasal polyps

CRSSNP: chronic rhinosinusitis without nasal polyps

microbiome: the totality of microbial organisms, or their genes, residing in a given niche (e.g., the nose and sinuses)

allergic fungal sinusitis (AFS):

a form of sinus disease associated with fungal colonization of the nose and sinuses

antrochoanal polyps: single polyps arising from the maxillary sinus and entering the nasal cavity

aspirin-exacerbated respiratory disease (AERD):

a syndrome characterized by comorbid asthma, nasal polyps, and sensitivity to aspirin-like drugs

COX1:

a cyclooxygenase enzyme responsible for prostaglandin synthesis

INTRODUCTION

Chronic rhinosinusitis (CRS) is a disease of inflammation of the nose and paranasal sinuses and upper airways characterized by 12 weeks of persistent symptoms including congestion, stuffiness, nasal discharge, pain or facial pressure, impairment or loss of the sense of smell (anosmia), cough, and fatigue. Although heterogeneous, investigators recognize two main forms, one with nasal polyps (CRSwNP) and one without (CRSSNP) (1, 2). Unremitting inflammation can last for years, and CRS affects approximately 12% of the population. Intranasal corticosteroids have limited effectiveness in CRS. It is accepted that the nasal microbiome is disturbed in CRS, and certain organisms, such as fungal species or *Staphylococcus aureus*, have been implicated in driving inflammation in some patients. Sinus disease (both acute and chronic) is the number one justification for the use of antibiotics, though these drugs have efficacy in only a subset of patients. After failure of medical management, patients often resort to surgical approaches to manage disease. Surgical removal of sinus tissues can aid drainage of sinuses filled with fluid (3). Tissues removed during surgery are of considerable value in laboratory-based investigations of pathologic mechanisms.

OVERVIEW OF FORMS OF CRS, EPIDEMIOLOGY, NATURAL HISTORY, AND COST

Heterogeneity in the pathology of CRS influences clinical phenotype, responses to treatment, and outcomes. CRSSNP comprises more than two-thirds of cases and is less likely to be managed by surgical intervention, whereas CRSwNP represents 20–25% of cases. Polyps are outgrowths of edematous inflammatory tissue that have grown into the middle meatus (see **Figure 1**). CRSwNP produces less pain and more facial pressure; it is more likely to cause anosmia, less likely to respond to antibiotics, and more likely to respond to corticosteroids (1, 2). A minor form of CRS is hyperplastic CRS, which has pathologic similarities to CRSwNP but without outgrowth of polyps. Another minor form of CRS is allergic fungal sinusitis (AFS), usually characterized by florid growth of a fungal organism, such as *Aspergillus* or *Alternaria* spp., resulting in local immune responses with eosinophilia and production of a characteristic thick mucin. Nasal polyp growth occurs in cystic fibrosis or as antrochoanal polyps, but these diseases are not referred to as CRS and are not considered in this review. A particularly severe form of CRS is known as aspirin-exacerbated respiratory disease (AERD), which is characterized by nasal polyps, asthma, and sensitivity to ingestion of aspirin or other COX1 inhibitors (4).

The annual cost of managing CRS in the United States alone is approximately \$8 billion, and the aggregate number of surgeries for CRS in general is nearly 500,000 per year (5). Up to one-third of patients require multiple surgeries, sometimes as many as a dozen surgeries over an extended period of time as the inflammatory tissue regrows. Based on incidence and prevalence, it can be concluded that CRS is a relapsing, remitting disease (2, 6). More men suffer from CRSwNP than women, although more women suffer from AERD than men (7).

NORMAL FUNCTION OF THE NOSE AND SINUSES

The nose protects the lungs by filtering and humidifying air prior to entry to the lungs (8). Dense collections of vascular sinusoids and distensible blood vessels termed capacitance vessels vary flow from one nasal passage to the other in a nasal cycle. Lateral or anterior serous glands generate secretions. The nose senses airborne volatile compounds via pattern recognition and olfactory receptors. Olfaction can be essential in avoiding exposure to toxins and pathogens in the air or food. The filtering function of the nose initiates immune sensitization to potential pathogens. Waldeyer's ring, a structural constellation that includes lymphoid tissue in the tonsils

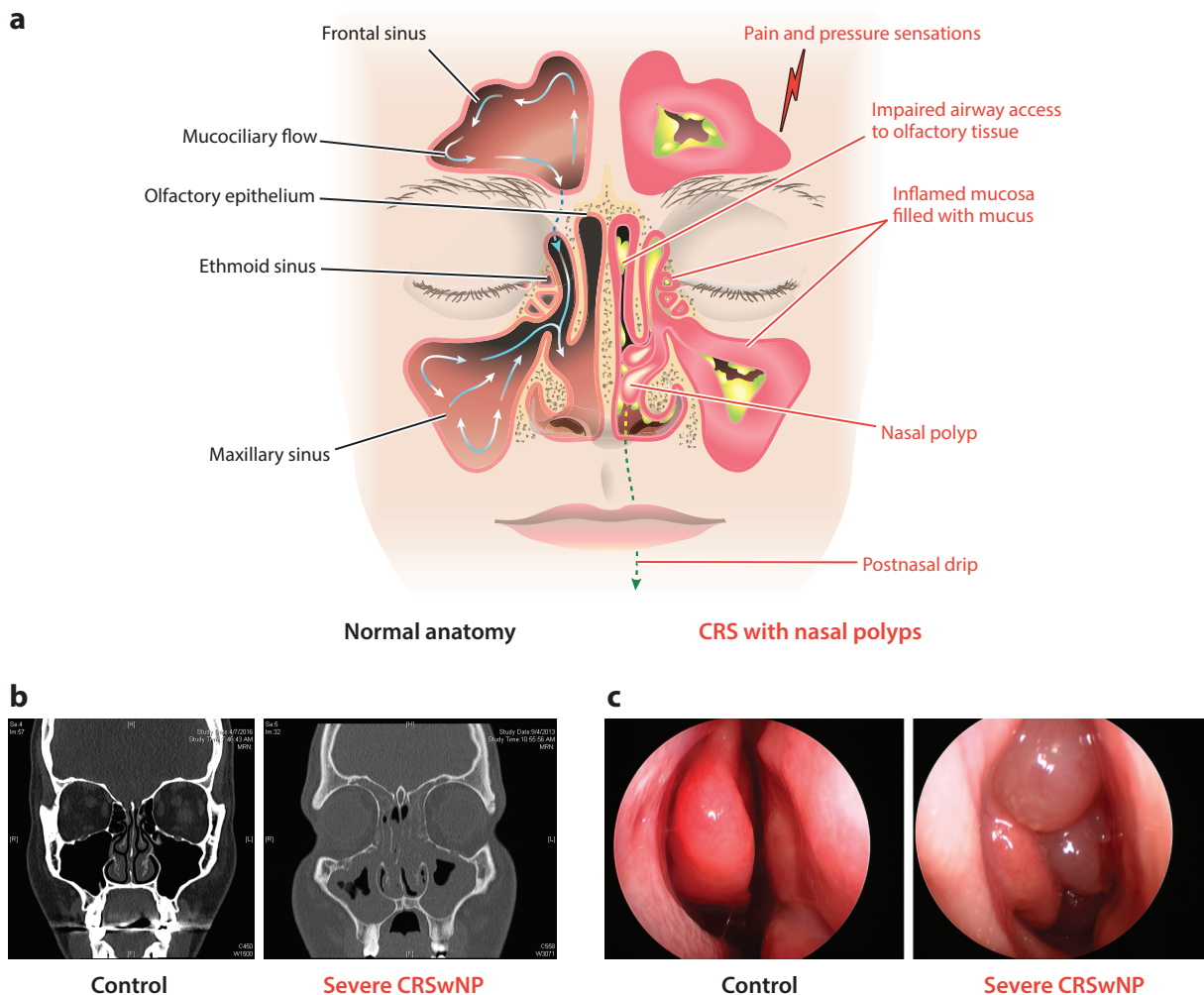


Figure 1

Panel *a*, overview of gross anatomical and inflammatory changes associated with chronic rhinosinusitis and illustration of the mucociliary flow pattern within the sinuses. Panel *b*, computed tomography images of a healthy person and one with severe chronic rhinosinusitis with nasal polyps (CRSwNP). Panel *c*, endoscopic images from a healthy person and from one with severe CRSwNP.

and the adenoid and submandibular lymph nodes, is an important sentinel portal for sensitization by respiratory pathogens (9). The pharyngeal tonsils (i.e., adenoids) are located in the roof of the nasopharynx, the tubal tonsils are at the outflow of the Eustachian tubes, and the palatine tonsils are located in the oropharynx. The mucosal epithelium of tonsils contains M cells that transmit antigens to the lymphoid structures. As seen in **Figure 1**, an orderly flow of mucosal surface fluid and mucus within the sinuses drains into the ostiomeatal complex; nasal and sinus

nasopharynx: the upper pharynx that connects with the nasal cavity

Eustachian tubes:

tubes involved in pressure equalization that link the inner ear with the nasopharynx

oropharynx: middle pharynx behind the mouth

M cells: specialized cells in the epithelium of lymphoid follicles that transport solute proteins for immune stimulation

ostiomeatal complex: channel that links the frontal, ethmoid, and maxillary sinuses to the middle meatus

nasal vestibule: anteriormost region of the nasal cavity

Lund-Mackay score: a scoring system to evaluate inflammation in the sinuses using computed tomography

ethmoid sinuses: sinuses located within the ethmoid bone that are a frequent site of nasal polyp growth

turbinate tissues: conch-shaped bony structures in the nasal passage

maxillary sinuses: large sinuses found below the eyes on the cheekbone

fluids are then swallowed. Trapped antigens enter the lymphatic systems and reach lymph nodes in the occipital, cervical, parotid, submental, and submandibular regions where they prime and expand populations of B and T lymphocytes that can later populate the alimentary or respiratory tracts. Epithelial cells on the mucosae as well as glands create an antimicrobial mucous blanket containing immunoglobulins, enzymes, antimicrobial peptides, and other factors important in innate host defense (10).

STRUCTURAL CHANGES IN THE NOSE AND SINUSES IN CRS WITH FOCUS ON POLYPS

The nose and sinuses undergo significant structural metamorphosis in CRS, as illustrated in **Figure 1**. The sinuses fill with inflammatory mucosal tissue as well as secretions. The olfactory zone is shown at the top of the superior meatus. Both obstruction and inflammatory events can lead to anosmia. **Figure 1b** shows opacification in a computed tomography (CT) scan of the sinuses and nasal vestibule of a CRS patient compared with a healthy subject; changes are quantified using an objective Lund-Mackay score (11). Endoscopic views in **Figure 1c** of a healthy control patient and a patient with CRSwNP show nasal polyps emerging from the ethmoid sinus through the ostium. In CRSsNP, sinus tissues and the nasal vestibule are swollen and copious secretions are observed, often with pus. Significant heterogeneity is observed macroscopically and microscopically, and underlying histopathologic mechanisms vary. **Table 1** represents an attempt to summarize findings about the general histologic features and cytokine expression in CRSsNP and CRSwNP, the latter divided based on presence of eosinophils. Notably, studies of gene expression, histopathology, or physical structure generally utilize control tissues from healthy patients undergoing surgery for noninflammatory indications. Control tissues used are variable, including inferior turbinate, uncinate, or ethmoid tissues, making comparisons among studies challenging (see **Figure 1**). Distribution of the forms of disease described in **Table 1** and the underlying pathologic manifestations vary by continent and race (see below).

TISSUE REMODELING AND POLYP FORMATION IN CRS

Early theories proposed that polyps are adenomas, fibromas, mucosal exudates; cystic dilations of excretory ducts; or swelling due to blockage of glands or lymphatics (12). Alternative theories suggested lymphangitis from recurrent infection or glandular hyperplasia as core causes. Tos and colleagues (12) described a model based on epithelial rupture and necrosis leading to protrusions from the lamina propria and epithelial repair. Many of these early theories identified mechanistic elements still held as important. Recent molecular studies identify emerging endotypes based on cytokine expression, implying multiple disease mechanisms (13, 14). Noneosinophilic disease is much more prevalent in Asian countries such as China, Korea, and Japan, although prevalence of eosinophilic disease has risen along with industrialization (see below). In addition to CRSwNP, other eosinophilic forms of disease include polyps associated with AERD, AFS, and Churg-Strauss disease, whereas noneosinophilic forms include cystic fibrosis (CF), antrochoanal polyps (usually single polyps growing out of the maxillary sinus), Young syndrome, and Kartagener syndrome-associated polyps. Early endotyping differentiated between edematous, fibrous, and cystic nasal polyps, though these terms are not used widely at present. Kountakis et al. (15) found that eosinophilic forms of both CRSwNP and CRSsNP, having more edema, were more severe than the corresponding noneosinophilic forms, whereas noneosinophilic forms have more glandular hyperplasia and dense collagen deposition. Independent of eosinophilia, fibrosis and

Table 1 Overview of chronic rhinosinusitis (CRS) heterogeneity and consensus of the literature regarding features, cells, and mediators present in tissues from patients with CRS without polyps (CRSsNP), eosinophilic CRS with polyps (E-CRS), and noneosinophilic CRS with polyps (NE-CRS). Note that the prevalence of the forms, features, cells, and mediators vary by geography and race

	CRSsNP	E-CRS	NE-CRS
Feature			
Fibrosis	Pronounced	Minimal	Minimal
Collagen deposition	Abundant	Minimal	Minimal
Edema	Minimal	Abundant	Significant
Glandular hyperplasia	Abundant	Outside of polyp	Outside of polyp
Pseudocyst formation	Not present	Present	Present
Cells			
Eosinophils	In some patients	Abundant	Present
Neutrophils	Abundant	Some present	Many present
Mast cells	Slightly increased	Increased	Somewhat increased
B cells/plasma cells	Few present	Abundant	Abundant
Basophils	Not present	Abundant	In some patients
Mediators			
IL-4, IL-5, IL-13	In some patients	Significant expression	Minimal expression
IFN- γ	In some patients	Minimal expression	Minimal expression
IL-17	In some patients	Expression in Asia	Expression
TGF- β	Increased expression	Minimal expression	Some expression
MMPs	MMP1, 2, 8, and 9	MMP1, 2, 7, 8, and 9	MMP1

Abbreviations: IFN- γ , interferon- γ ; IL, interleukin; MMPs, matrix metalloproteinases; TGF- β , transforming growth factor β .

collagen deposition are commonly seen in CRSsNP but not CRSwNP, whereas edema is a prominent feature of the polypoid forms of disease but less so CRSsNP. Van Bruaene & Bachert (16) have reported differences in tissue remodeling and patterns of cytokine expression in Belgium and China. A large histopathologic study of CRS in Wuhan, China, affirmed the link of eosinophilic infiltration with edema and the association of neutrophils with transforming growth factor β (TGF- β) and fibrosis (17). Hyperplasia of submucosal glands is common in nonpolypoid CRS but rare within nasal polyps themselves, especially in the eosinophilic forms. In nasal polyps, glandular density actually decreases significantly—a decrease associated with a stretching of the glandular canals and formation of tubular glands within the polyp tissue. Both forms of CRS have copious secretions, increased numbers of goblet cells, and activation of glands and goblet cells. Pseudocyst formation occurs in CRSwNP but is not generally observed in CRSsNP (18, 19).

Evaluation using trichrome or picrosirius staining shows increased collagen in CRSsNP but minimal expression in nasal polyps (less than control tissue in most cases) (20). These stains do not detect all collagen forms: In addition to fibrillar collagens (I, II, III, V, XI), there are short-chain forms (VIII, X), basement membrane forms (IV), multiplexins (XV, XVIII), fibril-associated forms (IX, XII, XIV, XVI, XIX), and membrane-associated forms (XIII, XVII), among others (20). Dr. Sergejs Berdnikovs at Northwestern has performed a multistudy analysis of nasal polyp microarray findings deposited in the Gene Expression Omnibus (GEO) database and has found significant elevations of mRNA levels in collagen X, VI, and VIII as well as lumican (S. Berdnikovs,

transforming growth factor β (TGF- β):
a member of a family of molecules involved in inflammation, remodeling, and fibrosis

pseudocyst: a lesion that is cystic in appearance but lacks epithelial and endothelial cells

lumican:
a proteoglycan involved in extracellular matrix formation

matrix metalloproteinases (MMPs):

proteases involved in degradation and remodeling of the extracellular matrix

fibronectin: an extracellular matrix protein that mediates cellular binding via integrins

laminin: an extracellular matrix component that comprises the basal lamina

elastin: an elastic protein component of connective tissue

occludin: a tight junction protein

vimentin: an intracellular filamentous gene expressed by mesenchymal cells

epithelial-to-mesenchymal transition (EMT): a process during which differentiated epithelial cells acquire mesenchymal features, such as motility and proliferation, often during the process of epithelial repair

M2 macrophages: a phenotypic state of macrophages stimulated by IL-4 or IL-13 involved in repair

acanthosis: hyperplasia of the epithelium

personal communication). Several studies have reported increased matrix metalloproteinase (MMP) levels that degrade the extracellular matrix (e.g., collagen, gelatin, fibronectin, laminin, and elastin), regulate many biologically active molecules, and modify tissue structure (**Table 1**) (19, 21–23). A polymorphism of MMP-9 has been reported to be a risk gene for CRS (24). Elevated levels of endogenous MMP inhibitors, tissue inhibitors of metalloproteinases (TIMPs), have also been described. Degradation by MMPs has been proposed to be important in pseudocyst formation (19).

Relatively few studies have attempted to enumerate the phenotypes of fibroblasts in CRS. One important study evaluated polyp histopathology during the growth process (25). Early stage polyps were collected with the entire stalk and pedicle from the middle turbinate and were compared with mature ethmoid polyps. Early stage polyps had more epithelial loss, whereas mature polyps had greater deficits in junctional proteins E-cadherin, zonula occludens-1 (ZO-1), and occludin. Early polyps had increased TGF- β , more vimentin staining, and elevated activated myofibroblasts that were α -smooth muscle actin (α SMA) positive, suggesting greater epithelial-to-mesenchymal transition (EMT) and ongoing repair. Early polyps also had more M2 macrophages and more fibronectin staining, reflecting more extensive type 2 inflammation. The stalk of the early polyps had extensive deposition of collagen, suggesting greater activation of fibroblasts early during polyp formation (25). Phenotyping by flow cytometry of fibroblasts isolated from CRS and control tissues using fibroblast specific protein 1 (FSP1, also known as S100A4) positive and mucin 1 (MUC1) negative staining phenotype found a hierarchy in fibroblast numbers: AFRS > CRSwNP > CRSsNP = Controls (26). Considering the low levels of typical collagen in polyps, determining whether polyp fibroblasts make atypical collagens is worthwhile. Fibroblasts isolated from nasal polyp tissue showed significantly enhanced expression of CXCL10 but only when the patients also had asthma. Higher expression of this chemokine has been proposed to contribute to virus-induced exacerbation of disease (27).

An alternative hypothesis by Takabayashi et al. (28, 29) explains nasal polyp growth by the deposition of fibrin mesh within the tissue. In this model, vascular leak leads to activation of thrombin via tissue factor and cleavage of plasma fibrinogen. Fibrin is crosslinked by Factor XIIIa derived from M2 macrophages in the tissue. Polyps have reduced fibrinolytic capacity resulting from impaired epithelial expression of tissue plasminogen activator (tPA) (28, 29). Reduced tPA and elevated M2 macrophages containing XIIIa result from increased expression of interleukin 13 (IL-13) in polyp tissue. Deposition of fibrin resulting from strong type 2 inflammation may be of benefit in immobilization and destruction of parasite worms (30, 31).

In the epithelium, one can observe both acanthosis and acantholysis in samples from patients with CRS. Within the tissue, vascular leak contributes to tissue swelling and formation of nasal polyps, as demonstrated by elevated presence of plasma proteins and clear edema. Reports of angiogenesis with increased levels of vascular endothelial cell growth factor (VEGF) and markers of blood vessel growth, along with increased blood vessels in polyp, are variable. The density of vessels within polyps may be similar to that in normal tissue, and expansion of vessels may parallel expansion of the tissue. A view of the mechanism of polyp formation, informed by newer data on cellular responses and based on the action of new generation biological drugs in eosinophilic CRSwNP, suggests that the infiltration, activation, and mediator release of eosinophils, mast cells, and basophils are important in polyp formation.

Epithelial Dysfunction in CRS: Ongoing Epithelial-to-Mesenchymal Transition and the Injury/Repair Cycle

Effective barrier function is essential for survival, and chronic compromise of the epithelial barrier is a characteristic feature of a number of important diseases. Together, the physical barrier, mucociliary escalator, and local innate antimicrobial responses compose what is sometimes

called the immune barrier. The main structures that maintain the physical barrier are the tight junctions and adherens junctions that make strong contacts between epithelial cells and the desmosomes/hemidesmosomes that anchor columnar cells to basal cells and basal cells to the basement membrane (32). Tight junctions contain ZO-1, occludin, and claudins as well as junctional adhesion molecule 1 (JAM-1) proteins. These transmembrane proteins adhere to each other by homotypic binding in the space between adjoining cells, and some have cytoplasmic domains attached to the actin cytoskeleton within the cell. Adherens junctions contain the transmembrane proteins E-cadherin and nectin and intracellular proteins α - and β -catenin, which maintain actin binding. Desmosomal attachments consist of heterotypic binding of desmoglein to desmocollin, which binds inside the cell to desmoplakin. Loss of barrier can result from genetic defects or reduced expression of barrier structural proteins resulting from injury, infection, or inflammation. For instance, prolonged loss of barrier in the skin can result from mutations in the tight junction protein claudin-1, leading to loss of barrier, increased susceptibility to sensitization, and atopic dermatitis (33). Defects in claudin expression or function are also important in a variety of gastrointestinal diseases (34). More relevant to airways inflammation and CRS, studies by Holgate and others have convincingly shown a role for defective lung epithelial barrier in asthma pathogenesis (35, 36).

An EMT occurs in mucosal and cutaneous barriers during inflammation and repair, and chronic EMT is observed in CRS, asthma, and cancer. During EMT, differentiated epithelial cells lose their typical morphology, polarity, and junctional attachments to one another, proliferate, and become spindle-shaped mesenchymal cells with migratory function. These mesenchymal cells, sometimes referred to as myofibroblasts, often traverse the lamina reticularis and synthesize collagens and other matrix proteins, expanding the size of the basement membrane. **Figure 2** illustrates changes in the expression of molecules that are biomarkers of the EMT process in CRS (35, 37, 38). For example, epithelial cells undergoing EMT lose expression of tight junction and adherens junction proteins, including ZO-1, claudins, occludin, and E-cadherin; the myofibroblasts that they become express matrix proteins, including desmin; fibronectin; collagens I, III, IV; tenascin; laminin; and elastin. These mesenchymal cells also express vimentin, MMP2 and MMP9, α SMA, and transcription factors associated with their differentiation, including Snail, Slug, and Twist. EMT can be induced by TGF- β , members of the EGF family, VEGF and FGF. Prominent signaling pathways inducing EMT include tyrosine kinase receptor pathways, the Notch pathway, SMAD pathways, and Wnt pathways (39). Other pathways initiating EMT include STAT3 as well as gp130-Src-YAP (40). The hormone-processing enzyme proconvertase 1 (PC1/3), usually only expressed in neuroendocrine tissue, is elevated in polyps and is expressed in basal epithelial cells in CRS but not in healthy control tissue. Overexpression of PC1/3 in an epithelial cell line induced profound EMT (41). One of the matricellular proteins expressed by epithelial cells in type 2 inflammation, periostin, has also been shown to be a potent activator of EMT by a TGF- β -dependent pathway, illustrating that diverse stimuli, including cytokines and adhesion substrates, can initiate the process (42). Myofibroblasts produce fibronectin, tenascin, and periostin and form a provisional matrix important in temporary protection from a breach in the epithelial barrier.

Several studies have shown a physical or functional defect in barrier in patients with CRS (43, 44). Soyka et al. (45) reported reduced barrier function in tissues from CRS patients. Many studies have confirmed the loss of epithelial markers and gain of mesenchymal markers in CRS (reviewed in 46). Markers shown in **Figure 2** in blue are epithelial markers that are lost in CRS, and those shown in red are mesenchymal markers that are gained in CRS. **Figure 2** also lists known inducers of EMT, including growth factors, cytokines, proteases, and other stimuli. Jang et al. (47) reported alterations in expression of both ZO-1 and E-cadherin, Shahana et al. (48) described epithelial damage in an EM study and reported shortening of desmosomes in polyp tissue from asthmatic

acantholysis:

loss of desmosome intercellular connections causing disruption and shedding of the epithelium

vascular endothelial cell growth factor (VEGF):

a cytokine that induces vascular leak and growth (angiogenesis)

mucociliary

escalator: the combined action of cilia moving a mucous blanket through the sinonasal spaces and into the nasopharynx

tight junctions:

junctional structures that tightly bind epithelial cells and reduce intercellular permeability

adherens junctions:

intercellular junctions that attach epithelial cells to each other and to the cytoskeleton

desmosomes:

structures involved in intracellular adhesion in epithelia

hemidesmosomes:

structures involved in adhesion of epithelia to the matrix

zonula occludens

(ZO-1): a protein component of tight junctions

claudins: proteins that constitute tight junctions in differentiated epithelial cells

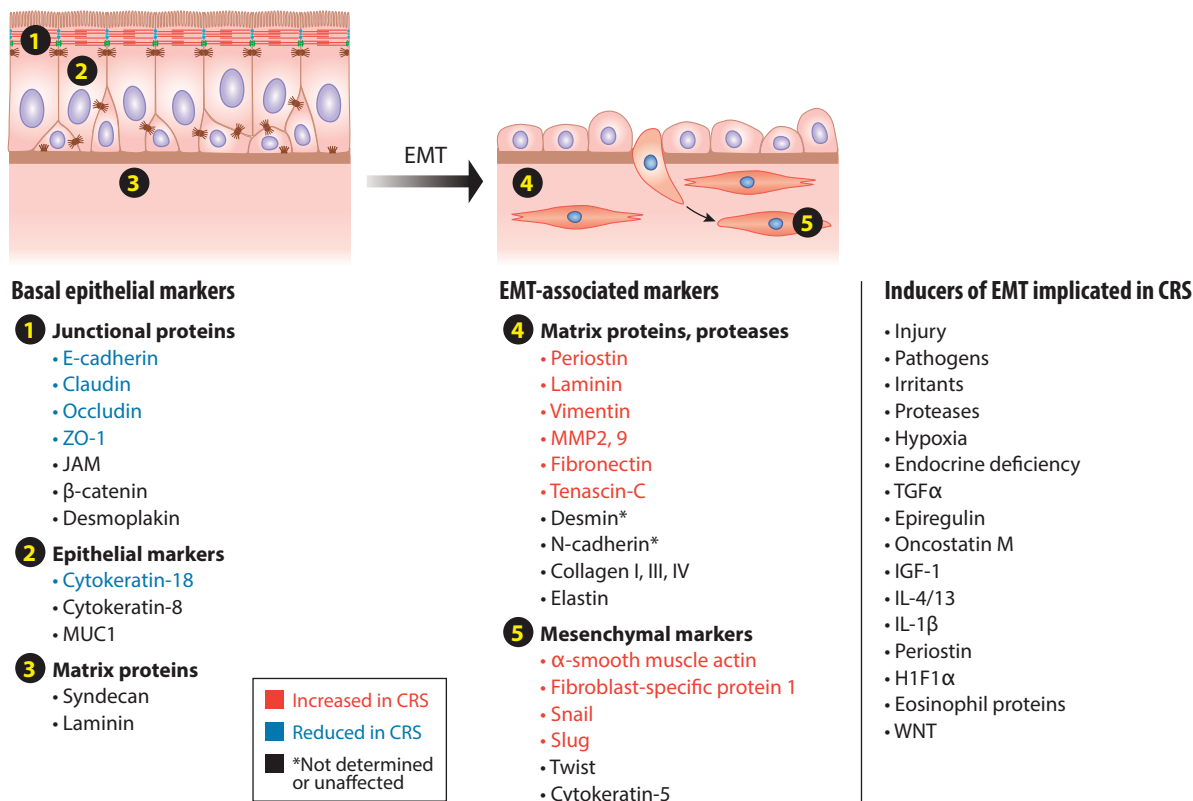


Figure 2

Tabulation of some of the important biomarkers of differentiated healthy epithelium (*left*) and epithelium undergoing repair-associated epithelial-to-mesenchymal transition (EMT) (*right*). Markers shown in blue on the left are reduced in chronic rhinosinusitis (CRS), and markers shown in red on the right are increased in CRS. The literature strongly supports the existence of an ongoing, chronic EMT response in CRS. Shown on the far right of the figure are some known EMT inducers that have been implicated in CRS. Abbreviations: H1F1 α , hypoxia inducible factor-1-alpha; IGF-1, insulin-like growth factor-1; IL, interleukin; JAM, junctional adhesion molecule; MMP, matrix metalloproteinases; MUC1, mucin 1; TGF- α , transforming growth factor α ; ZO-1, zonula occludens.

E-cadherin:

a structural component of adherens junctions involved in intercellular adhesion in epithelia

nectin: adhesion molecules involved in adherens junctions

desmoglein:

a structural component of desmosomes that mediates epithelial cell adherence

patients, Rogers et al. (49) reported reductions in claudin-1 and occludin in polyps, and Meng et al. (25) found that mature polyps have reduced ZO-1, occludin, and E-cadherin. Epithelial loss was highest in early stage, middle turbinate polyps compared with mature ethmoid polyps, and α SMA was lower in mature polyps (25). Interestingly, more EMT was found in the stalk of early stage polyps than in the body of the early stage polyp or in the body of mature polyps, suggesting that the stalk is an important site for the EMT process, which would agree with the higher deposition of collagen in the stalk (25). The same pattern was observed with staining for vimentin and the TGF- β signaling molecule pSMAD, i.e., it was in the stalk rather than the body of the early stage polyps (25). Hupin and colleagues (50) reported decreased E-cadherin in CRS, along with decreased cytokeratins and vimentin; the vimentin expression correlated with basement membrane thickness and eosinophils in the tissue. They observed increased thickening in basement membrane in both CRSwNP and CRSsNP.

The underlying causes of the EMT process in CRS are not known and could be related to many of the inducers shown in **Figure 2**. Respiratory allergens containing proteases can disrupt

the barrier and initiate EMT (51–53). Protease 1 from *Dermatophagoides pteronyssinus* disrupts tight junctions and degrades ZO-1 and occludin (53). Decreased levels of serine protease inhibitor Kazal-type 5 can contribute to loss of barrier in skin and have been found in the nasal epithelium in CRS (54, 55). In a mouse asthma model, extended exposure to house dust mite antigen (HDM) caused thickening of smooth muscle along with loss of E-cadherin and occludin and gain in vimentin, α SMA, and procollagen 1 associated with the induction of Snail1, a transcription factor that drives many of these EMT changes (51). Similar changes in HDM-induced allergic rhinitis are observed in patients (52). Stimulation of human bronchial epithelial cells in vitro with HDM increased vimentin and fibronectin and slightly decreased E-cadherin due to EGF signaling (56). Shin et al. (57) demonstrated that hypoxia induces many EMT changes, and hypoxia inducible factor 1 (HIF1 α) levels correlated with loss of E-cadherin and gain of α SMA in polyp tissues in vivo. Hypoxia also induces MUC5AC via a HIF-1 α -dependent mechanism. Smoking is another factor that worsens CRS in patients and is now known to induce EMT based on studies in patients with chronic obstructive pulmonary disease (58). The type 2 cytokines IL-13 and IL-4, found at high levels within eosinophilic polyps, may act as inducers of chronic EMT in CRS (45). These type 2 cytokines decrease electrical resistance, JAM-A, and E-cadherin of differentiated epithelial cultures (45). As discussed in another section below, treatment of CRSwNP patients with anti-IL-5 to reduce eosinophilia shrinks nasal polyps (59). An important article by Flood-Page et al. (60), who studied anti-IL-5 in asthmatic patients, showed a marked reduction in several EMT markers, including tenascin, lumican, and procollagen III in the reticular basement membrane. This finding suggests that eosinophils and their products are important in barrier dysfunction, damage, and induction of EMT in the airways. An overview of hypothetical dysregulation of the injury–repair cycle in CRS, and its impact on epithelial barrier function, is shown in **Figure 3**.

Epithelial Dysfunction in CRS: Mucociliary Dysfunction

Proper mucociliary function is essential in nasal physiology and immunity (61). Ciliary motion through the sol phase of the mucus blanket propels mucus and the trapped microbes and particulates out of the sinuses and nasal airways. Mucociliary function in CRS can be tested using the saccharine test, which measures mucociliary movement of saccharine from the sinuses into the mouth where it is tasted. The majority of early studies found that mucociliary function is impaired and that the degree of impairment of clearance is correlated with the severity of CRS (reviewed in 62). Most studies have found that ciliary beat frequency (CBF) is in the normal range in CRS patients. Not surprisingly, studies of the viscoelasticity of mucus yielded variable results, likely depending on the proportions of gel and sol phase, the purulence of the mucus, the hydration of the mucus, etc. Because CRSsNP is often characterized by frequent infections/colonization of the sinonasal cavity with bacteria, it is important to note that several bacteria commonly associated with CRS, including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*, produce toxins that are ciliostatic or ciliotoxic (63). Many studies have reported loss or inactivity of cilia in CRS tissue due to ciliary injury. Defects in mucociliary function promote bacterial growth and formation of biofilms, creating a vicious cycle. Chen et al. (62) found normal resting CBF in CRS explants with a marked defect in the increase of CBF in response to stimulation with ATP, possibly due to desensitization of purinergic receptors or a decrease in signaling molecules such as Ca²⁺, adenylyl cyclase, or protein kinase A. Alterations of CBF-activating factors, including cytokines like tumor necrosis factor (TNF) and IL-1 β and autacoids like bradykinin or substance P, and changes in pH and temperature may be relevant (63). Cilia length in tissue sections and cytospin preparations was nearly double in CRS patients compared with normal tissues. The cilia also showed signs of damage and disorganized structure, and their number per cell was increased

desmocollin:

a structural component of desmosomes that mediates epithelial cell adherence

desmoplakin:

a structural component of desmosomes that mediates epithelial cell adherence

lamina reticularis:

one of the laminar layers that form the epithelial basement membrane

tenascin: extracellular matrix glycoprotein involved in provisional matrix

periostin:

multifunctional provisional adhesion molecule that supports integrin binding

Mucin 5AC

(MUC5AC): a mucus proteoglycan produced by goblet cells and submucosal glands

Junctional adhesion molecule A (JAM-A):

a protein involved in intercellular epithelial tight junction adhesion

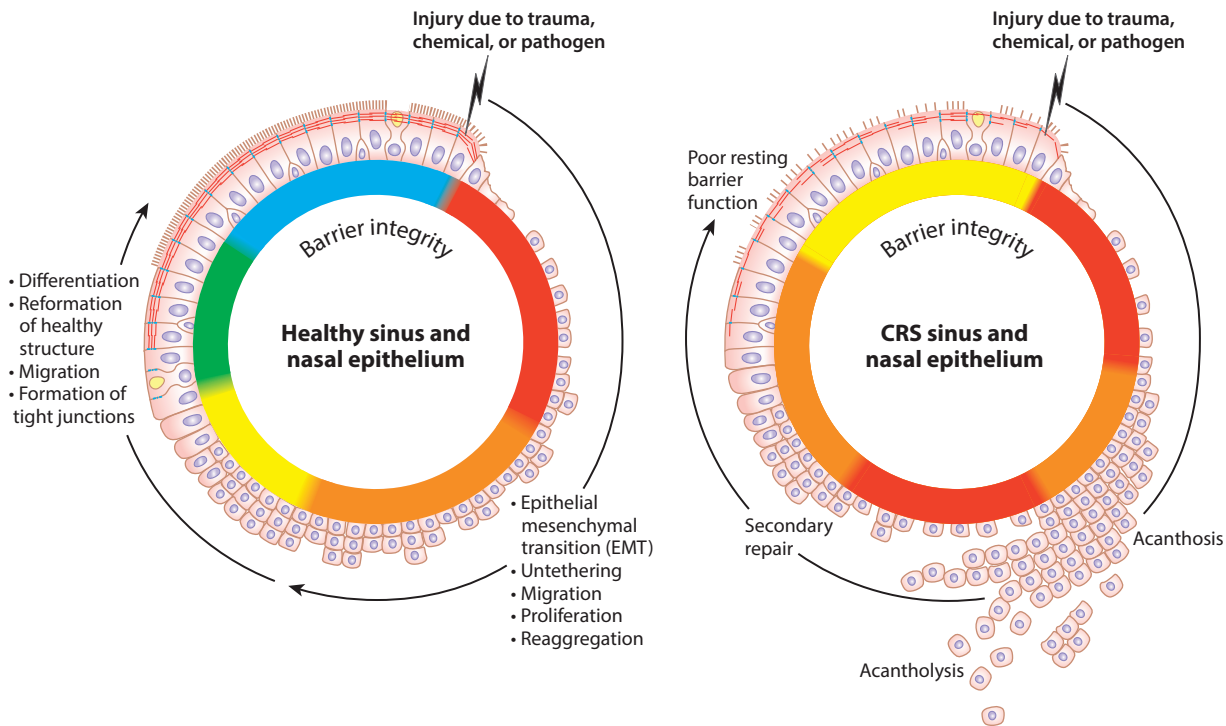


Figure 3

Epithelial dysfunction in chronic rhinosinusitis (CRS). A normal injury–repair cycle is shown on the left, illustrating loss of differentiation and polarity of epithelial cells associated with migration, proliferation, and reformation of junctional structures with neighboring epithelial cells. Epithelial permeability is indicated by the color on the basolateral side of the mucosae, with red indicating significant leak and green indicating a tight barrier. Changes in the injury–repair cycle hypothetically associated with CRS are shown on the right.

and therefore overly dense (64). Forkhead box protein J1 (Foxj1), a transcription factor involved in elongation of cilia and cilia density on cells, and centriolar coiled-coil protein of 110kDa (CP110) and TAp73 (a member of the p53 tumor suppressor family), factors involved in initiation and execution of assembly of cilia, were overexpressed in CRS, and levels correlated with cilia length. Thus, both ciliary injury and an abnormal upregulation of ciliogenesis leading to impairment of ciliary architecture and function have been found in CRS (64). The increased cilia length, asymmetry, and disorganization as well as overexpression of CP110, Foxj1, and TAp73 were stable in epithelial stem cells expanded in vitro and matured to air-liquid interface monolayers, suggesting either a genetic or epigenetic intrinsic defect (64).

Epithelial Dysfunction in CRS: Antimicrobial Responses

More than 100 molecules are involved in pathogen recognition and killing, most of which are expressed by the epithelium in the upper airways and sinuses (see **Table 2**). Not surprisingly, many of these molecules are highly induced in CRS. Although not all have been evaluated, a few have been reported to be dysfunctional or reduced at the mucosal surface in CRS, as indicated in red within **Table 2** and discussed here. The reader is also referred to reviews discussing the host–microbe interactions in CRS (55, 65–67).

Toll-like receptors. Toll-like receptors (TLRs) play fundamental roles in innate immunity, are expressed by epithelial cells and immune cells in the nose and sinuses, and activate expression of

Toll-like receptors (TLRs): a family of receptors involved in recognition of pathogen-associated molecular patterns

Table 2 Pathogen recognition structures that mediate innate immunity. Those shown in red text have at least one member reported to be reduced in CRS

Type of structure	Protein family	Number of members in the family
Recognition receptors	Toll-like receptors (TLRs)	10
	Nod-like receptors (NLRs)	22
	TAS2R	25
	RLRs	4
	CD14	NA
	Cytosolic DNA sensors	12
Antimicrobial peptides	S100 proteins	18
	α-Defensins	7
	β-Defensins	39
	Cathelicidin (hCAP-18)/LL-37	NA
	Collectins	9
	Pentraxins	8
Endotoxin-binding molecules	LBP-BPI-PLUNC	12
	AOAH	NA
Enzymatic mediators	Lysozyme	NA
	Lactoferrin	NA
	Peroxidase/thiocyanate	NA
	Complement	NA

Abbreviations: AOAH, acyloxyacyl hydrolase; BPI, bactericidal/permeability-increasing; CD14, cluster of differentiation 14; LBP, lipopolysaccharide binding protein; LL-37, member of the cathelicidin antimicrobial peptide family; PLUNC, palate lung nasal epithelial clone; NA, not applicable.

inflammatory mediators and host defense molecules (68–70). Many studies have evaluated TLR expression in CRS but without consensus, as some studies have reported increased levels of one or more TLRs (71–73) and some have reported reduced levels or no differences (68, 72, 74, 75). Most studies used PCR and evaluated surgical tissue, which has variable expression, and studies using relatively pure primary epithelial cells collected by scraping or brushing are needed. Two studies of single-nucleotide polymorphism (SNPs) in TLR genes have been done, one of which reported a SNP associated with increased risk of CRS in a Korean population (76).

Bitter taste receptors. Bitter taste receptors such as T2R38 detect quorum sensing molecules produced by gram-negative bacteria in biofilms such as acyl-homoserine lactone compounds (77). These ligands activate T2R38-induced Ca^{2+} responses in primary nasal epithelial cells and in specialized solitary chemosensory cells (SCC), leading to increased mucociliary function, production of the antimicrobial gas NO, and rapid release of antimicrobial peptides such as β-defensin 2 (77–79). Polymorphisms in T2R38 underlie the lack of ability to taste various bitter compounds in food, and the nonfunctional allele of T2R38 (AVI) is a risk allele for disease severity in CRS and CF (80–82). It is not known whether allelic variants in the 25 other T2Rs influence CRS risk or whether T2R38 is unique (83). The sweet receptor that detects glucose, T1R 2/3, can suppress the protective response of T2R38, and elevated nasal glucose-mediated T2R suppression may explain why patients with diabetes mellitus are 3–4 times more likely to be infected with *P. aeruginosa* and gram-negative rods (79, 84). Insulin is an essential hormone for growth of epithelial cells, however, and subclinical defects in insulin signaling may be associated with barrier defects and increased

bitter taste receptors: a family of seven transmembrane spanning receptors that mediate the sensation of bitter taste and innate immune responses

defensin: an antimicrobial peptide family produced by inflammatory and structural cells

LBP: an LPS-binding protein that participates in activation of the LPS receptor

TLR4: a receptor that mediates inflammatory responses to endotoxin

PLUNC: palate, lung, and nasal clone family of innate host defense molecules

BPI: bactericidal/permeability increasing proteins, a family of innate immune receptors

eotaxins-1, 2, and 3: chemokines that bind to CCR3 and recruit eosinophils and other inflammatory cells

acyloxyacyl hydrolase (AOAH): an enzyme that catabolizes and neutralizes bacterial endotoxin (LPS)

S100 proteins: a family of proteins that exert regulatory, inflammatory, and/or host defense functions

risk for CRS as suggested by Berdnikovs and colleagues (H. Abdala-Valencia, L.F. Loffredo, I. Martinez Reyes, K.A. Erickson, M. Browning et al., unpublished manuscript).

Endotoxin-binding molecules. The LBP-BPI-PLUNC family of molecules is important in innate immune responses to lipopolysaccharide (LPS or endotoxin) derived from gram-negative bacteria: LBP binds LPS and collaborates with CD14 for the activation of TLR4, and most BPI-PLUNC proteins bind to bacteria and LPS and mediate opsonization, direct killing, neutralization of LPS, disruption of biofilms, or other antimicrobial actions (85). A proteomic analysis of polyp tissue and normal tissue found reduced levels of PLUNC, confirming results of immunohistochemical analysis (86). Two forms of PLUNC were identified in lavage fluid and were decreased after exposure to irritants such as tobacco smoke (87). Seshadri et al. (88) analyzed PLUNC family members and found decreased levels of LPLUNC2 and SPLUNC1 in nasal polyp tissue attributable to reduced submucosal glands in polyps. Interestingly, two other family members, BPI and LPLUNC4, were reduced in uncinate tissue, suggesting a global defect in expression in CRS (88). Although Wei et al. (89) reported that reduced PLUNC was seen only in eosinophilic polyps and not in noneosinophilic polyps in China, Tsou et al. (90) showed decreased PLUNC associated with colonization of bacteria, especially *S. aureus* and *P. aeruginosa*. Knockout of the *SPLUNC* gene in mice led to significant enhancement of eosinophilic inflammation in an OVA challenge model, and SPLUNC protein blocked LPS induction of eotaxin-2 by alveolar macrophages (91). Another endotoxin-binding protein that is of interest in CRS is acyloxyacyl hydrolase (AOAH), an LPS-catabolizing enzyme shown to be genetically associated with asthma and CRS (92, 93). Considering the importance of gram-negative organisms in CRS, further advancement of our understanding of the role of reductions in BPI-PLUNC members and AOAH is in order.

Antimicrobial peptides. Several S100 proteins are antimicrobial and also promote inflammation. Levels of mRNA for S100A7 and S100A8/S100A9 were found to be lower in nasal epithelial cells from CRS patients, and protein was reduced in nasal lavage fluids (54, 94, 95). S100A7 is also lower in lavage fluid from patients with allergic rhinitis (96). The heterodimer of S100A8/S100A9, known as calprotectin, is also expressed by neutrophils and consequently calprotectin levels are highly elevated within sinonasal tissue and polyps due to neutrophil recruitment (95, 97). Levels of S100A8/S100A9 decrease in nasal lavage fluid of CRS patients with age (98).

Enzymatic mediators. Lysozyme and lactoferrin have been reported to be either depleted or increased in various sinonasal tissues in CRS (99, 100). However, both are clearly reduced in the epithelium of nasal polyp tissue, owing to large reductions in submucosal glands in polyps (88). In addition, methacholine challenge studies have shown decreased lysozyme release in CRS patients (101). Studies of CRS with biofilm formation have also reported diminished lactoferrin, and a proteomics study reported diminished lysozyme in lavage (102, 103). Due to the loss of glands, it can be predicted that all glandular host defense molecules will be reduced in nasal polyp tissue (88). A study of complement components and complement activators showed that 19% of 87 CRS patients had a complement deficiency (mostly mannose binding lectin deficiency), whereas only 10% of 150 control patients did (104). It is notable that activation of complement occurs in CRS and is probably important in pathogenesis (see below).

INNATE AND ADAPTIVE INFLAMMATORY RESPONSES UNDERLYING THE PATHOGENESIS OF CRS

Several recent reviews have focused on inflammation, cytokines, T and B lymphocytes, and innate lymphoid cells (ILCs) in CRS pathogenesis (13, 30, 66, 105). The goal of this section is therefore to primarily provide an overview of major findings and conclusions in the literature.

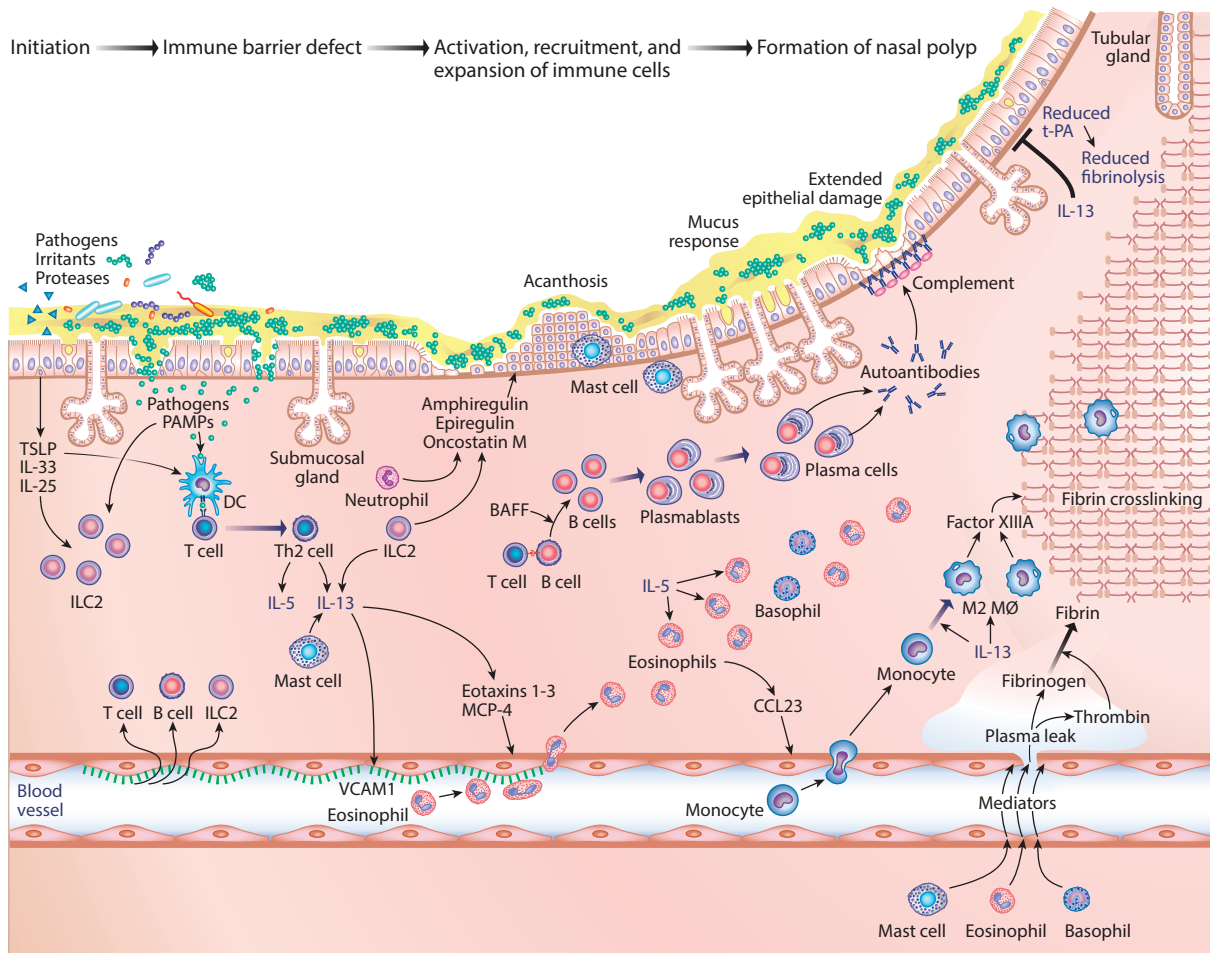


Figure 4

Hypothetical timeline and interactions of events in the formation of nasal polyps. (*Left*) The damaged epithelium responds to injury from pathogens, proteases, and irritants. Abbreviations: BAFF, B cell-activating factor; CCL23, chemokine (C-C motif) ligand 23; DC, dendritic cell; IL, interleukin; ILC2s, type 2 innate lymphoid cells; MCP-4, chemokine (C-C motif) ligand 13, also known as CCL13; PAMP, pathogen-associated molecular patterns; Th2, T helper cell type 2; tPA, tissue plasminogen activator; TSLP, thymic stromal lymphopoietin; VCAM1, vascular cell adhesion molecule 1.

When rapid local innate immune responses are insufficient to prevent growth or entry of pathogens, adaptive immune T cells and B cells are activated and recruited to reinforce the response. **Figure 4** describes elements of innate and adaptive immunity that are activated in CRS and speculates as to how they interact temporally in the formation of nasal polyps. The damaged epithelium responding to injury from pathogens, proteases, and irritants is shown. Although the injured epithelium makes at least three T helper cell type 2 (Th2)-promoting cytokines, IL-25, IL-33, and TSLP, among these three TSLP is most highly induced in CRS tissue (106–108). Along with the mast cell products PGD₂ and leukotrienes, TSLP can activate type 2 innate lymphoid cells (ILC2s) (109). In the presence of TSLP, ILC2s and mast cells express substantial quantities of type 2 cytokines, especially IL-5 and IL-13, and relatively little IL-4 (110). This pattern is the

interleukin 25 (IL-25): a cytokine that promotes ILC2 cell responses
interleukin 33 (IL-33): a cytokine that promotes ILC2 cell responses

thymic stromal lymphopoietin

(TSLP): a cytokine that induces ILC2 responses

type 2 innate lymphoid cells

(ILC2s): immune cells that produce type 2 cytokines without direct antigen stimulation

amphiregulin:

a member of the EGF family that stimulates epithelial proliferation and repair

oncostatin M:

member of the IL-6 cytokine family that reduces epithelial barrier

epiregulin: a member of the EGF family that stimulates epithelial proliferation and repair

B cell-activating

factor (BAFF): an activating factor of the TNF family, a B cell proliferation and activation factor

vascular cell

adhesion molecule 1 (VCAM-1): an endothelial adhesion molecule that mediates recruitment of VLA4 positive inflammatory cells

MCP-4: also known as CCL13, a chemokine that binds to CCR3 and recruits eosinophils and other inflammatory cells

same as seen in nasal polyps, suggesting a role of ILC2s in the type 2 cytokine production in CRSwNP (111). Unlike T cells, ILC2s do not require antigen for activation, and they rapidly mobilize these cytokines. Elevated ILC2 levels have been reported in polyp tissue (112–114). ILC2s also promote epithelial repair via the production of amphiregulin (115). Acanthosis seen in CRS may be attributable to local production of amphiregulin, oncostatin M, epiregulin, and other inducers of EMT (116, 117).

Epithelial injury may allow pathogen-associated molecular patterns and antigens from mucosal pathogens to cross the barrier and initiate recruitment and activation of antigen-specific T and B cells. Moving left to right in the model, type 2 cytokines from ILC2 are important in recruitment of adaptive immune cells by activation of endothelial adhesion molecules, induction of production of chemokines, and provision of cytokines that shape T cell differentiation. The nature of the ILC that is activated shapes the T cell response; in this case, ILC2s promote Th2 responses (110). Eosinophilic polyps contain type 2 cytokines, whereas noneosinophilic polyps generally do not (**Table 2**). In parallel with an expansion of T cells in CRSwNP, there is an impressive expansion of B cells, plasmablasts, and plasma cells (118, 119). Local activation, proliferation, class switch recombination, and production of antibodies take place within polyps (118–120). Little is known about the antigen specificity of T or B cells in CRS. IgE antibodies to aeroallergens and staphylococcal enterotoxin have been reported (121). Tan et al. (122) showed that nasal polyps contain autoantibodies that are likely responsible for activation of complement in the tissue. Among the autoantibodies described are antibodies directed against basement membrane, and the complement activation that occurs is localized at the basement membrane region (123, 124). The presence of autoantibodies in polyps may occur as a result of significant levels of the B cell-activating factor (BAFF), a cytokine that drives autoimmunity in mouse models of overexpression (125).

A comprehensive summary of cytokines present in CRS has been compiled by Hulse et al. (30). Whether type 2 cytokines are derived from ILC2, Th2 cells, or mast cells and basophils, the importance of IL-5 and IL-13 in formation of polyps is convincing. Bachert, Gevaert, and colleagues have shown that antibodies against either IL-5 or the IL-4/IL-13 receptor alpha chain shrink polyps (59, 126). As shown in **Figure 4**, IL-5 and IL-13 drive many features of the inflammation and the effector cell recruitment that is characteristic of the disease. IL-13 activates endothelial expression of VCAM-1 and other adhesion molecules that recruit lymphocytes, eosinophils, and basophils, and IL-13 also induces the expression by the epithelium and other cells of the C-C motif chemokine receptor 3 (CCR3)-specific chemokines that recruit mast cells, eosinophils, and basophils, including C-C motif chemokine ligand 13 (MCP-4, also known as CCL13) and eotaxins-1, 2, and 3, into the tissue. Once eosinophils are recruited to the tissue, IL-5 promotes their survival and activation (127). Activation of mast cells triggers the release of serous and mucous secretions by goblet cells and glands. IL-13 is also important in differentiation of recruited monocytes to become M2 or alternatively activated macrophages. Kato and colleagues (128) showed that chemokine (C-C motif) ligand 23 (CCL23) is highly elevated in polyp tissue and is produced by eosinophils. This chemokine binds CCR1 and recruits monocytes that differentiate to M2 macrophages. IL-13 suppresses expression of tPA and induces Factor XIIIa to promote accumulation of fibrin mesh using thrombin and fibrinogen derived from plasma leak induced by mediators from mast cells, basophils, and eosinophils (28, 29; see also **Figure 4**). The figure applies to eosinophilic polyps, the type 2-driven primary form of polypoid CRS found in North America, the United Kingdom, and Europe and a secondary form found in Asia (**Table 2**). Several reports have shown the presence of elevated IL-17 in some polyps from patients in China and Japan, correlating with eosinophilia (129–131). The M2 macrophage response, fibrin deposition, and IgE and autoantibody responses could possibly be restricted to type 2 inflammation in nasal polyps (132).

Whether there are defects in regulatory T cells in CRS is controversial. Although reports have shown reduced levels of the regulatory T cell (Treg) transcription factor Forkhead box P3 (FOXP3) and reduced FOXP3⁺ staining in polyp tissues, no change in Tregs was detected by flow cytometry in another study (133–135). Treg activation in peripheral blood cells is reported to be reduced in CRS patients compared with control patients, but most studies do not find reduced levels of the suppressive cytokines IL-10 or TGF- β (136–139). Studies in noneosinophilic patients in Asian countries have shown increased presence of IL-17–producing FOXP3⁺ Tregs (134, 140, 141). On balance, CRS cannot be attributed to defects in Treg responses at present.

Treg: regulatory
T cell

RACE, EOSINOPHILIA, AND CRS: WHAT ARE THE ROLES OF GENES AND THE ENVIRONMENT?

To date, no large-scale studies have been performed to identify genetic linkages and polymorphisms that drive CRS pathogenesis. Because the average age of onset of CRS is over 40, building pedigrees and evaluating inheritance has been challenging. Recent studies of the Utah population database (UPDB) analyzed families of more than 25,000 patients with CRS and determined that first-degree relatives (parents, children, and siblings) of CRSwNP patients had a 4.1-fold increased risk of CRS, whereas first-degree relatives of patients with CRSsNP had a 2.4-fold risk (142). Second-degree relatives of CRSwNP and CRSsNP patients had 3.3-fold and 1.4-fold risks, respectively. A similar UPDB study of eosinophilic esophagitis (EE) found a 3.4-fold risk of EE in first-degree relatives (143). Although large studies of primary care CRS patients are lacking, a few family studies and a large number of relatively small studies of surgical patients support a genetic basis of inheritance of CRS (reviewed in 82, 144). Most studies used candidate gene approaches, were underpowered, and still await replication. Findings of genetic associations/linkages worthy of special mention include the identification of the cystic fibrosis gene, *CFTR*, as a risk gene. *CFTR* was shown to be present in 7% of CRS patients, versus 2% of the general population, and was confirmed in a linkage study performed in a Hutterite population (145, 146). As discussed above, Cohen and colleagues (77, 81) have identified polymorphisms in the bitter taste receptor T2R38 that exert a strong genetic effect on susceptibility to CRS. Two genome-wide association studies using pooled samples identified associations with matrix proteins laminin α 2, laminin β , as well as AOA (147). Other interesting genes identified were thyroid hormone receptor interactor (*TRIP2*) and neuron navigator 3 (*NAV3*). The association with AOA was confirmed using a similar approach in a study of Chinese CRS patients and control patients (93). Several studies have shown associations with HLA genes, innate immune genes, and cytokines (82, 144).

The presence of eosinophils in CRS tissues was recognized shortly after the work of Ehrlich identifying dyes that bind to eosinophil granules, and eosinophil granule proteins have been linked with pathology (148, 149). Correlations between disease severity and eosinophils measured in blood or nasal tissues are well established. The Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC), a 15-center retrospective study in Japan, evaluated eosinophils in the blood and tissue of 1,716 patients who had sinus surgery and concluded that blood eosinophils, ethmoid disease, asthma, and aspirin intolerance were all associated with recurrence of disease and need for further surgical intervention (150). The importance of eosinophils in asthma has been known for decades, and assessment of sputum eosinophil content has significant utility in treatment choice for asthmatic patients (150). Eosinophils have both inflammatory and tissue remodeling effects, and their derived mediators can damage epithelial cells, stimulate EMT, activate or suppress sensory nerves, modulate the activity of stem cells and plasma cells, and alter mechanical responses of airways (151–153). Tan and colleagues (154) took biopsies from the superior meatus, where the olfactory zone resides, and found a strong correlation

between eosinophils in that area and anosmia. Indeed, olfactory dysfunction has been shown to be greater in patients with eosinophilic disease and/or asthma (154, 155). Antibodies directed against IL-5 or the IL-4/IL-13 receptor alpha chain reduce eosinophils and shrink polyps in CRSwNP, supporting a role of eosinophils in CRSwNP pathogenesis (59, 126). These drugs also restore olfactory function, supporting the hypothesis that eosinophils mediate anosmia (see below).

Nasal polyp tissues removed from CRS patients during surgery in Asian countries, including China, Korea, and Japan, have fewer eosinophils than tissues from CRS patients collected in Europe and the United States (reviewed in 156). However, Kim et al. (157) studied two similar groups of 230 patients in Korea, one in 1993–1994 and another in 2010–2011, and found that the eosinophil counts rose from 6.8 per high-powered field to 19.3 during this time. In general, less than 50% of polyps in Asian countries are eosinophilic, whereas approximately 75% of polyps in Europe and the United States are eosinophilic (149, 156, 158, 159). In Japan, the JESREC study found a prevalence of eosinophilic polyps similar to that in Western countries, and several other studies suggest that the degree of eosinophilia in polyps in Japan, China, Malaysia, Korea, etc. is increasing (150). Adoption of a Western lifestyle is one possible factor driving this change, suggesting that there are strong environmental influences on eosinophilia (150).

Eosinophilia correlates strongly with type 2 immune and inflammatory responses, and patients with eosinophilic polyp disease, whether in the East or the West, generally have higher levels of IgE, higher prevalence of atopy, and greater prevalence and severity of asthma (156). Periostin is a provisional matrix protein produced during EMT (see above) that is highly induced by IL-4 and IL-13 and therefore has been used increasingly as a marker of Th2 inflammation. In a study of serum levels in 190 asthma patients in Japan, those with high levels of periostin had more aspirin intolerance, nasal polyposis, blood eosinophilia, and reduced lung function, although they did not have increased atopy (160). A study by Cao et al. (132) in China found that polyp tissue from patients with eosinophilic inflammation had higher IgE against aeroallergens and increased mast cell activity, independent of atopy. Local generation of specific IgE in nonatopic subjects, or so-called entopy, was proposed to explain the dissociation of skin test reactivity from presence of local antigen-reactive mast cells in the eosinophilic polyp tissues.

Many findings suggest that genetics plays a strong role in eosinophilia. Eosinophilic polyps compose only 25% of polyp cases in the Asian-American population compared with two-thirds to three-quarters of polyps from African-American, Caucasian, and Hispanic populations, suggesting that genetic or cultural/dietary factors lead to reduced eosinophilia (161). Like CRS, EE has a strong familial association, with nearly 10% of parents of EE patients having a history of esophageal disease. Rothenberg and colleagues (161, 162) reported 26 multiplex families with EE and demonstrated a large familial risk of EE in both dizygotic twins and non-twin siblings. Based on the prevalence of EE in the general population (5/10,000), the risk for siblings was increased approximately 80-fold, compared with a 2-fold increased risk for atopy in the same group, leading them to conclude that genetics has a large role in eosinophilia. Environmental factors that might influence eosinophilia include birth season, breastfeeding, and antibiotic use during infancy; these are considered risk factors that may alter the microbiome (162, 163).

Although asthma studies show very strong influences of race on outcomes, few studies have examined the influence of race on CRS outside of Asian and Caucasian populations (164, 165). A study of three major national surveys in the United States (National Health Interview Survey, National Ambulatory Medical Care Survey, and National Hospital Ambulatory Medical Care Survey) found that 90% of published studies contain little or no information on race. Minority endoscopic sinus surgery patients made up only 18% of the total in the United States, despite an expected percentage of 35%, leading to the conclusion that insurance status influenced the result (166). A retrospective cohort study of CRS cases treated in a large urban center in Chicago found

that African-American CRS patients were at higher risk for anosmia, and those requiring functional endoscopic sinus surgery had a higher prevalence of nasal polyposis, AERD, and olfactory loss and had worse CT scores of their sinuses. Those African-American CRS patients with polypoid disease had a history of more hospitalizations for asthma. These findings suggest that African-Americans, who are known to have higher prevalence and worse severity of asthma, also have worse CRSwNP than patients from other races (167). Pinto et al. (168) reported that African-American CRS patients had lower vitamin D levels than control African-American patients, and Bush et al. (169) reported that surgical outcomes were not as durable in African-American patients with polypoid CRS and asthma compared with Caucasian patients. Based on the foregoing, as well as information on asthma, it seems likely that CRSwNP is worse in African-Americans, Puerto Ricans, and Hispanics than in Caucasians and Asians, but clearly more studies are needed (164, 165).

ROLE OF THE NASAL MICROBIOME IN THE DEVELOPMENT OF CRS

Sinusitis is the single-highest indication responsible for antibiotic use, and several hypotheses implicate microorganisms in CRS. The fungal hypothesis proposes that allergic sensitization to fungi by T cells induces response to ambient fungi and drives type 2 disease (170). Although antifungal agents failed to manage CRS in most studies, it is not clear if these drugs would be effective if ambient fungi drive disease (171). Bachert and colleagues (172) have advocated a strong role for colonization with *S. aureus* in driving CRS, especially severe disease with polyps. Despite associations of disease severity and chronicity with *S. aureus* colonization, with IgE against *S. aureus* antigens and enterotoxins and with elevation of V β -bearing T cells potentially expanded by enterotoxins supporting this hypothesis, colonization by *S. aureus* is not observed in all or even most CRS patients. Another hypothesis implicates bacteria that form biofilms in driving CRS disease (173, 174). Yet another hypothesis, which has good support, is that respiratory viruses such as rhinovirus and influenza are responsible for seasonal exacerbations of CRS, which occur largely in the late fall and winter (175). Thus far, microbiome studies have not identified a single causative agent associated with disease; the main findings demonstrate increased abundance and decreased diversity of the nasal microbiome in CRS (176, 177). It is clear that bacteria, fungi, and viruses all can play a role in subsets of patients with CRS and that there is not a single microbial organism that can be implicated.

UNMET NEED FOR EFFECTIVE THERAPEUTIC APPROACHES TO MANAGEMENT OF CRS

In patients who fail medical management, surgery can open the ostia that drain and clear the sinuses and can unblock the nasal passages by removing nasal polyp tissue (3). It can often dramatically improve symptoms, as measured by the Sino-Nasal Outcome Test 22 questionnaire, restore olfaction, and reduce the need for other medications (3). The disease often relapses, and approximately 20% of surgeries performed are revision surgeries. Over a 12-year period, 80% of patients have relapse and 37% undergo revision surgery (178). It is not uncommon for patients with severe nasal polyposis to have had more than 10 prior surgeries, indicating an unmet need for new effective treatments for CRS.

New classes of drugs have been developed for asthma and other diseases that have potential utility in CRS. Bachert, Geveart, and collaborators (59, 126, 179) have performed double-blind clinical trials on omalizumab, mepolizumab, and dupilumab, all of which were able to shrink nasal polyps and improve symptoms. These drugs, which, respectively, block the action of IgE on mast cells and basophils, IL-5 on eosinophils, and IL-4/IL-13 on a host of cells, have great promise for managing intractable type 2 CRSwNP. They also establish the importance of mast

cells (and/or basophils) and eosinophils in the pathogenesis of CRSwNP. Other possible strategies to target inflammatory cells in CRS include the following: an anti-Siglec-8 antibody that inhibits mast cell function and induces eosinophil apoptosis; a GATA3 DNzyme that targets ILC2 and Th2 cells; inhibitors and cytotoxic antibodies against DP2, otherwise known as CRTH2, a PGD receptor important in type 2 skewing; reslizumab and benralizumab, two other antibodies targeting eosinophils; lebrikizumab and other IL-13–targeting antibodies; and many others (180–186). Recently, inhibitors of Jak-STAT signaling, so-called Jakinibs, have had great success in managing inflammatory diseases such as rheumatoid arthritis and are worth evaluation (186). Topical application of inflammatory drugs is challenging due to the difficult access to sinus mucosae, but new advances in topical drug applications, via both implantable devices and new formulations that maintain prolonged elevations of drug levels in the sinonasal cavities, are promising.

CLOSING REMARKS

Important questions remain to challenge CRS researchers: Are nerves involved in producing inflammation or pathogenesis, or are the physical manifestations, such as anosmia, cough, reflexive secretory responses, and headache, all just consequences of the illness? What are the factors that drive polyp formation in noneosinophilic disease? Are submucosal glands passive victims of the process that leads to formation of tubular gland structures, or does dysfunction of glands drive the formation of polyp tissue? What are the activators of ILC2, and is eosinophilic CRS an innate inflammatory disease? What are the antigens that activate T and B cells, and is CRS an adaptive inflammatory disease? Is the barrier defect seen in CRS due to genetic defects in the epithelium? Is the injury–repair cycle associated with EMT, acanthosis, and acantholysis a consequence of inflammation, a cause of inflammation, or both? Will ongoing clinical trials soon inform us of the relative importance of effector cells, including eosinophils, mast cells, basophils, neutrophils, and ILC2s, in driving the inflammatory manifestations? CRS is a heterogeneous illness with high prevalence, cost, and impact on quality of life; it is essential that active investigations answer these and more questions and pursue new strategies for treatment.

DISCLOSURE STATEMENT

R.P.S. has consulted over the last two years on topics relevant to CRS with Astra Zeneca, Genentech, GSK, Intersect ENT, Merck, Regeneron, UCB and Sanofi. R.P.S. is a founder and advisor of Allakos, which has an ongoing clinical trial in CRS.

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