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# Perspectives on the etiology of chronic rhinosinusitis

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## Abstract

**Purpose of review—**This article reviews recent insights surrounding the etiology and pathogenesis of chronic rhinosinusitis. In particular, we highlight the increasing recognition of host-mediated mechanisms in driving mucosal inflammation.

**Recent findings—**Published differences between epithelium from patients with chronic rhinosinusitis and normal controls can be classified into several broad categories. Alterations are reported in the various components of the epithelial innate immune system including epithelial-expressed pattern-recognition receptors (PRRs) and the levels of antimicrobial innate immune effector molecules. Other studies demonstrate differences in the proteins involved in maintaining epithelial barrier integrity. Finally, recent studies show in chronic rhinosinusitis that epithelial-derived cytokines, chemokines and inducible surface proteins are involved in recruiting and activating cells of the adaptive immune system.

**Conclusion—**The sinonasal epithelium provides a mechanical and innate immune barrier to a diverse array of environmental agents. This barrier also plays a key role in regulating the acquired mucosal immune response in the nose. Recent studies suggest that defects in this barrier may foster development of chronic sinonasal inflammation in response to environmental agents, and pathogenic or commensal organisms. The ability to dissect and analyze defects in the inflammatory response in rhinosinusitis may help identify novel targets for drug development.

### Keywords

acquired immunity; barrier dysfunction; epithelium; inflammation; innate immunity; rhinosinusitis

## Introduction

Chronic rhinosinusitis (CRS) is a clinical syndrome associated with persistent inflammation of the mucosa of the nose and paranasal sinuses. Objective evidence for mucosal inflammation using nasal endoscopy and/or computerized tomography (CT) is required for confirmation of the diagnosis [1]. The definition of CRS is intentionally inclusive, encompassing, for example, both the polypoid (CRSwNP) and nonpolypoid (CRSsNP) forms of the disease but does not address causation or etiology.

Historically, CRSsNP was considered to result from an incompletely treated case of acute infectious rhinosinusitis resulting in chronic infection. CRSwNP was considered a distinct,



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noninfectious disorder of unclear etiology, perhaps related to atopy. Research over the last 30 years suggests that the etiology of CRS is complex and multifactorial and the concept of chronic mucosal inflammation has supplanted infection to describe the disorder, but this shift still neglects the issue of etiology [2•]. In a minority of CRS cases, distinct host genetic or systemic disorders such as Kartagener's syndrome, cystic fibrosis (CF), Wegener's granulomatosis and sarcoidosis are identified as the cause of sinonasal inflammation. The overwhelming majority of CRS cases, however, are idiopathic and specific proposed mechanisms for persistent inflammation include obstruction of the osteomeatal complex, impaired mucociliary clearance, osteitis, atopy and microbial resistance, including biofilm formation [3]. These potential pathogenic mechanisms form the underpinnings of most current therapies for CRS, which include antimicrobials, antihistamines, leukotriene antagonists, topical and systemic corticosteroids, and endoscopic sinus surgery for restoring mucociliary clearance and drainage through the osteomeatal complex [4]. Although these therapies are effective at helping the majority of patients, significant variability remains in both the efficacy and durability of the clinical response, highlighting current limitations in our understanding of this disorder. This review will briefly summarize recent attempts to identify a common underlying pathogenic mechanism in CRS and provides a detailed description of emerging evidence highlighting epithelial host defects as central factors in CRS etiology and pathogenesis.

## Fungal hypothesis and superantigen hypothesis

Over the last decade, two dominant hypotheses attempted to broadly explain CRS etiology as a response to common intranasal organisms: the *Alternaria* 'fungal hypothesis' and *Staphylococcus aureus* (*S. aureus*) 'superantigen hypothesis'. The relative merits of these hypotheses were recently reviewed [2•]. Briefly, the 'fungal hypothesis' suggests that an excessive host response to the common airborne fungus *Alternaria* is the primary pathogenic trigger in all forms of CRS, both polypoid and nonpolypoid, varying only in intensity [5,6]. It suggests that *Alternaria* not only induces the immunologic response via T cells, but these organisms also serve as the targets of eosinophils with resultant degranulation and tissue destruction [7]. The primary evidence in support of the fungal hypothesis is the relative hyperreactivity of peripheral blood mononuclear cells (PBMCs) from CRS patients in response to stimulation with supraphysiologic doses of *Alternaria* antigen [6]. Presumably, this heightened response reflected an immunologic sensitization to *Alternaria*, suggesting it was particularly important in inciting the CRS inflammatory response. However, the majority of the patients (78%) studied had concurrent asthma, and the heightened responsiveness of the PBMCs may reflect this latter disorder [5]. Furthermore fungi, particularly *Alternaria*, contain intrinsic proteases that can nonspecifically activate protease-activated receptors (PARs) present on the cell surface. Hence, exposure of activated PBMCs to high levels of proteases may account for the heightened in-vitro responses via non-antigen-specific effects, rather than by a directed response against *Alternaria* antigens [2•, 8•]. Nonspecific effects of a protease may not be inconsequential, however, given that epithelial-based PARs are known to be upregulated in CRS [2•,8•,9]. In summary, though high levels of *Alternaria* or other fungi may have direct immunostimulatory effects, we still lack convincing in-vitro or in-vivo evidence indicating that fungal antigens are the targets of the mucosal T cell or B cells in CRS [8•]. Therefore, despite initial enthusiasm for the fungal hypothesis as the basis for all chronic sinus disease, the current state of basic science evidence coupled with the failure of clinical trials with amphotericin [10•] indicates that a central role for fungi in CRS remains uncertain [2•,8•,11].

The superantigen hypothesis proposes that colonizing *S. aureus*, which is found more frequently in patients with CRSwNP, secrete superantigenic toxins that can foster the characteristic tissue response seen in polyps from CRSwNP patients [12]. In support of this

hypothesis, approximately 50% of CRSwNP patients demonstrate B and T cell responses consistent with superantigen exposure [13–21]. Thus far, there is no evidence of a role for superantigens in CRSsNP, suggesting a distinct but perhaps overlapping etiology and pathogenesis. The widespread prevalence of *S. aureus* nasal colonization [22] along with the unknown mechanisms underlying host susceptibility lead most investigators to view *S. aureus* superantigens, as a disease modifier rather than an etiologic agent [2•].

## Immune barrier hypothesis

Although the fungal and superantigen hypotheses are often presented as opposing or competing viewpoints, they essentially agree on one salient feature: both imply that unnamed host factors determine disease susceptibility to common environmental elements. The concept of a dysfunctional host–environment interaction actually forms the basis of one line of current research into CRS etiology and pathogenesis. The host sinonasal epithelium serves as the site of interface with inhaled irritants, commensal organisms and pathogens. Mucociliary clearance, physical exclusion, and the innate and acquired immune responses are used to separate host from environment. Broadly speaking, when components of these defenses fail, chronic mucosal inflammation ensues and the CRS syndromeis the symptomatic result. This line of thought gives rise to an immune barrier hypothesis of CRS, wherein host defects are the key to etiology and pathogenesis.

The shifting emphasis away from environmental and microbial agents toward identifying host susceptibility is well established in other chronic inflammatory diseases involving epithelial surfaces such as atopic dermatitis, psoriasis, asthma and inflammatory bowel disease (IBD) [23•,24,25]. Theoretically, the primary susceptibility could reside in the host acquired immune system, such as in T cell subsets for example, but epidemiologic research into CRS suggests that its incidence is not strongly correlated with other inflammatory conditions outside the airway, suggesting that susceptibility specific to the airway epithelium is more likely (unpublished data Chandra *et al.*). Recent studies in psoriasis, atopic dermatitis, asthma and inflammatory bowel disease have focused interest on the epithelium with polymorphisms and expression-changes found in genes encoding proteins associated with epithelial structure and function [26••]. This review summarizes recent emerging evidence that the sinonasal epithelial interface plays a similar role in the development of CRS, and dysfunction or dysregulation of epithelial-based mechanisms may provide a potential unifying theme in the etiology and pathogenesis of CRS.

### Physical barrier defects in chronic rhinosinusitis

In several chronic mucosal inflammatory diseases, accumulating evidence demonstrates that the breakdown of the mechanical component of epithelial barrier function can play an important role in permitting foreign proteins to stimulate an immune response [27]. In CRS, evidence for barrier disruption includes significantly diminished tight junction proteins and increased ion permeability when compared with normal controls [28,29]. More recently, studies in our laboratory demonstrated that *SPINK5*, which encodes the protein LEKT1, a protease inhibitor involved in maintaining epithelial barrier function, is significantly decreased in CRS [30•]. Genetic mutations in *SPINK5* are shown to be responsible for Netherton syndrome, a rare autosomal recessive condition that results in flaky skin, fragile hair and severe atopy [31]. Lower levels of protease inhibitors like LEKT1 in CRS epithelium may result in increased susceptibility to endogenous and exogenous protease activity [32•]. Interestingly, dust mites, fungi and bacteria all have significant intrinsic protease activity [2•,33,34], which in the presence of deficient endogenous protease inhibitors like LEKT1 may render the mechanical barrier more vulnerable to protease attack. Breakdown of the mechanical barrier may in turn allow greater mucosal penetration of

foreign proteins and subsequent magnification of the inflammatory response either through antigenic stimulation or through stimulation.

In addition to mechanical barrier maintenance, antiproteases such as LEKT1 protect epithelial surface receptors (protease-activated receptors or PARs) from excessive stimulation by exogenous proteases. This excessive PAR stimulation could at least theoretically trigger increased cytokine and chemokine production, cellular recruitment and, potentially, skewing of the subsequent acquired immune response [9,26••,35]. Together, these findings suggest that the integrity of the mechanical barrier and the complex interplay between proteases and antiproteases may have prominent roles in the development of many forms of CRS. Host defects in the proteins that underlie these processes may predispose to the development of CRS, particularly when challenged by high levels of environmental proteases present in bacteria, fungi and some allergens.

## Innate immune dysfunction in chronic rhinosinusitis

The human immune response is composed of two overlapping components, innate and acquired, both of which play critical roles in host defense. The innate immune system comprises cells and their associated mechanisms that provide the first line of defense against pathogens through genetically encoded pathways with limited specificity for molecular structures. In addition to the physical barrier and pathogen clearing effects of the mucociliary clearance system, sinonasal mucosa has been shown to express a vast arsenal of antimicrobial molecules [36]. In general, earlier studies of CRS did not demonstrate consistent alterations in the expression of these antimicrobial molecules, with increased levels reported in some molecules, whereas others are reportedly decreased [37–39]. A recent observation in our laboratory however, suggested that the S100 proteins might play a significant role in mediating some forms of CRS. The S100 proteins have multiple effects on cell differentiation and barrier function and several members (e.g. S100A7, S100A8 and S100A9) act as classic antimicrobial proteins with direct antibacterial and antifungal effects, recruit neutrophils and lymphocytes, and also aid in wound healing [40,41]. We recently reported that S100A7, S100A8 and S100A9 are substantially reduced in CRS when compared with controls [30•,32•]. Taken together, these studies suggest that diminished S100 proteins in sinonasal epithelial cells may predispose to development of CRS, possibly through increased microbial colonization or diminished wound healing [32•].

In addition to expressing secretory antimicrobial proteins, sinonasal epithelial cells express pattern-recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) [42–44]. Prominent among the PRRs are the Toll-like receptors (TLRs) that, when activated, trigger a pro-inflammatory response through the activation of nuclear transcription factors such as NF-kB, AP-1 and IRF3 [26••]. Given that TLR2, TLR3, TLR4 and TLR9 are expressed in the airway it is likely they play an important role in mediating host inflammation, with potential derangements contributing to the development of CRS [45]. This hypothesis is supported by the quantitative increase in TLR2 mRNA seen in cystic fibrosis polyps as well as in CRSsNP, at least in some studies [46,47], as well as reported decreases in mucosal TLR2 and TLR9 mRNA in samples from CRSwNP [48,49]. Overall, the data that support quantitative or qualitative derangements in TLR signaling associated with the development of CRS are inconsistent; this remains a theoretical mechanism that can account for chronic mucosal inflammation needing further exploration.

An important inducer of innate immune responses is the cytokine IL-22 that is secreted by Th17 and Th1 cells and activates epithelial cells via the IL-22 receptors (IL22R) [50,51]. In CRSwNP, the levels of IL22R1 were found to be significantly decreased in nasal polyposis when compared with controls, suggesting a diminished IL-22 response in CRSwNP [52]. IL-22 and its receptor work through the transcription factor STAT3, and emerging research

into the inflammatory responses in other sites such as the bowel and lung indicate that this pathway may be the critical cytokine in regulation of inflammatory responses at the epithelial interface in general [53–55]. This provides an interesting paradigm in which decreased IL-22R on nasal epithelial cells may impair innate immune responses in CRSwNP.

Together these data suggest that important facets of the innate immune system and its regulatory mechanisms may be impaired in CRS. Whether this results in impaired pathogen clearance, commensal overgrowth and dysregulation of the host inflammatory response is under investigation; however, altered expression of the above-mentioned genes, and altered performance of the molecular networks they maintain, could, at least theoretically, predispose to CRS.

## Activation of adaptive immunity through epithelial-mediated mechanisms in chronic rhinosinusitis

Epithelium also serves as an important mediator in recruiting and activating the adaptive immune system through multiple mechanisms. Firstly, epithelial cells mediate communication between the environment and adaptive immune system through cell surface molecules capable of directly engaging and regulating activation of T cells. Secondly, epithelial cells produce potent soluble cytokines such as BAFF, TSLP and interferon (IFN)-γ that activate B cells, dendritic cells and T cells respectively. Third, epithelial cells produce chemokines that attract and enable the migration of cells of the adaptive immune system [45]. Lastly, as discussed earlier, epithelial cells can secrete and respond directly to cytokines secreted by the cellular immune system such as IL-22 [56,57]. Nasal epithelial cells, therefore, appear to be central in responding directly to exogenous stimuli and mediating crosstalk with other cells types involved in the mucosal immunity. Dysfunctional or dysregulated interactions between epithelium and these other cell types may be pivotal in the subsequent development of CRS.

Key targets for nasal epithelial crosstalk are the dendritic cells found in abundance in nasal epithelial tissue that function as antigen presenting cells gathering and processing peptides from the environment to present to T and B cells [58]. One key airway epithelial protein is TSLP, which can be strongly induced by common viruses such as rhinovirus [59]. High levels of TSLP trigger dendritic cell-mediated polarization of the helper cell response in a Th2 direction [60••]. Furthermore, recent studies suggest that the absence of protease inhibitors like LEKT1 (see above) may increase TSLP production [35]. This suggest the hypothesis that diminished LEKT1 levels in CRS, mentioned earlier, may accentuate the TSLP response of epithelial cells to rhinovirus, accounting for the heightened Th2 response characteristic of some forms of CRS. Although elevated levels of TSLP in CRSwNP have not been demonstrated at the protein level, this attractive hypothesis may serve to link protease activity at the epithelial surface with the generation of a Th2 response.

Nasal epithelial cells also appear to interact with B cells and accumulating evidence suggests that B-lymphocytes are critical mediators in a growing number of chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. In the airway, localized differentiation of B-lymphocytes into plasma cells and localized, lymph node independent, class switch recombination are thought to play particularly important roles in the pathogenesis of allergic diseases of the airway such as allergic rhinitis and asthma [61•]. We have recently shown that BAFF (also called BLys or TNFSF13B) mRNA and protein levels are highly elevated in nasal polyp tissue in CRSwNP in comparison with CRSsNP, control and unaffected tissue in CRSwNP[62••].Wefound that BAFF is produced by epithelial cells and could be induced by stimulation by several cytokines and TLR3[63,64]. BAFF is a potent stimulator of B cell proliferation and class switching in B cells [65] and

may account for the germinal center like follicles, high numbers of plasma cells and increased levels of immunoglobulin (Ig)A found in nasal polyp tissue. Although these mechanisms may account for the increased B cells, plasma cells and immunoglobulins in nasal polyposis, the nature of the antigen specificity and any potential role for the secreted immunoglobulins in the pathogenesis of nasal polyposis remain unclear. It should be remembered, however, that IgA is an extremely potent trigger of eosinophilic degranulation, so this immunoglobulin may be key to local mediator release within polyp tissue [66]. These findings suggest that dysregulated BAFF production by nasal epithelial cells may distort the acquired mucosal immune response and play a role in polyp formation.

Increased numbers of total T cells and activated T cells are found in the inflammatory infiltrate of CRS and particularly in the nasal polyps in CRSwNP and cystic fibrosis. Several groups have investigated the nature of these infiltrating T cells through examination of the unique transcription factors utilized by T cell subtypes. These studies suggest that, in CRSwNP, there is a decrease in T-regulatory (Treg) responses as FOXP3, the primary transcription factor in Treg cells, was decreased relative to controls along with transforming growth factor (TGF)-β the main cytokine secreted by Treg cells [67•,68,69]. Nasal polyps with a more eosinophilic infiltrate had higher levels of the Th2-specific transcription factor GATA-3, whereas the newly identified neutrophilic nasal polyps in Chinese populations showed higher levels of Tbet, a transcription factor characteristic of Th1 cells [67•]. The mechanisms by which these various T cell populations are activated and recruited to the nasal mucosa are still under investigation, but epithelial cells may play a direct role in directing the inflammatory response [49,70].

## Future directions

The etiology and pathogenesis of complex disorders such as CRS are unlikely to be dependent on single genetic defects. CRS is probably best understood as a disorder driven by one or more defective molecular networks [71]. These molecular networks may be disturbed by genetic, epigenetic or environmental factors [49,70] and defects in one or more of these networks will likely account for the full range of phenotypes seen in clinical disease [71]. Although the immune barrier hypothesis provides a unifying umbrella, future goals include identifying the relevant molecular networks, how they correlate with phenotype and, lastly, where we can intervene. Although the current data are scant, the potential links between diminished S100 proteins, apparent increased microbial colonization with increased protease stress, diminished antiproteases (LEKT1), excessive TSLP with Th2 skewing, BAFF-induced IgA excess, and eosinophil degranulation are intriguing.

## Conclusion

Recent research is demonstrating that host responses mediated at epithelial surfaces play an important role in passive innate immunity, barrier exclusion and regulating the acquired immune response. The failure of any one of these functions due to genetic predisposition, epigenetic changes or environmental modifiers is postulated to result in chronic inflammatory responses that are observed in many disease states. Until recently, research into CRS has focused on pathogens and not the epithelial barrier as the mediator of inflammation, but emerging evidence suggests that barrier dysfunction, innate immune dysregulation and inappropriate activation of the acquired immune system are active processes in the pathogenesis of CRS. Together, these lines of evidence suggest that CRS should no longer be considered in exclusion of other chronic mucosal inflammatory conditions, and unraveling these host mechanisms will provide new strategies for targeted therapies in this disease.

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•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 61).

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