

Pathophysiology of chronic rhinosinusitis with nasal polyp

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ABSTRACT

Background: Chronic rhinosinusitis (CRS) is a common inflammatory condition of the paranasal sinuses and nasal passages. CRS with nasal polyp (CRSwNP) is a subtype of CRS, and the pathogenesis of CRSwNP remains largely unclear.

Methods: This article reviews the literature regarding the pathophysiology of CRSwNP.

Results: Evidence suggests that altered innate immunity, adaptive immunity, tissue remodeling, and/or effects of microorganisms may play a role in the development of CRSwNP. Aberrant arachidonic acid metabolism may also contribute to the pathogenesis of CRSwNP in patients with aspirin-exacerbated respiratory disease.

Conclusion: There have been significant advances in the understanding pathophysiology of CRSwNP. Additional research is needed to elucidate these mechanisms and to determine their relative importance in the pathogenesis of CRSwNP.

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Chronic rhinosinusitis (CRS) is defined as an inflammatory condition of the paranasal sinuses and nasal passages that persists for a minimum of 12 weeks.^{1,2} In the United States, CRS affects ~16% of adults annually, is responsible for an estimated \$5.8 billion/year of direct medical expenditures,³ and substantially impacts quality of life.⁴

CRS has been divided into two different phenotypes: CRS without nasal polyp (CRSsNP) and CRS with nasal polyp (CRSwNP). CRSsNP accounts for the majority of CRS cases (~60%), whereas CRSwNP accounts for 20–33% of cases.⁵ CRSwNP is more likely than CRSsNP to be associated with asthma, aspirin-exacerbated respiratory disease (AERD), and allergic fungal rhinosinusitis (AFRS). AFRS is characterized by evidence of immunoglobulin E (IgE)-mediated fungal allergy and thick inspissated allergic mucin containing fungal hyphae⁶; it has been suggested that AFRS is immunologically distinct from CRS.⁶ Further discussion of AFRS is beyond the scope of this article but is available elsewhere.^{1,6}

Despite the prevalence and morbidity of CRS, the pathophysiology of CRS remains largely unclear. Furthermore, the phenotypic differences between CRSwNP and CRSsNP may signify distinct pathogenic mechanisms. This article reviews significant advances in the understanding of the pathophysiology underlying CRSwNP. A review of the differential diagnosis and pathophysiology of CRSsNP will be presented elsewhere in this journal.

ROLE OF MICROORGANISMS IN CRSwNP

Unlike acute rhinosinusitis, the role of microorganisms in the pathophysiology of CRS (with or without nasal polyps) remains unclear.^{1,7} Research on microorganisms in CRS has focused primarily on identifying potentially pathogenic bacteria, as well as elucidating the role of biofilms, *Staphylococcus aureus* superantigens and fungi in

the pathogenesis of CRS. Studies of microorganisms specific to CRSwNP are very limited, but available data suggest that the microbiology of CRSwNP and CRSsNP appears similar.⁸

Bacteriology of CRSwNP

Both the bacteriology of CRSwNP and the clinical significance of CRSwNP bacteriology remains subject to debate. This controversy is caused by in part significant variation in sampling and culture methods among studies.^{1,9} Furthermore, reportedly similar microbiological flora in both diseased and nondiseased sinuses in patients with unilateral CRS disease questions the pathogenicity of isolated bacteria.⁷ Nevertheless, organisms that have been implicated as potential pathogens in CRSwNP (with potentially synergistic effects) include *S. aureus*, *Streptococcus pneumoniae*, viridans streptococci (*Streptococcus mutans*), *Moraxella catarrhalis*, and *Haemophilus* species.^{1,9–19} Coagulase-negative *Staphylococcus* has also been isolated frequently from CRS patients but is found in healthy subjects as well,^{9–13,15,20} so its pathogenicity in CRSwNP is even more uncertain. In contrast, Gram-negative enteric rods including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Escherichia coli*, and *Enterobacter* species are rarely found in healthy patients but have been recovered in several studies of CRS patients.^{1,10–12,15,21} It remains unclear if the presence of Gram-negative enteric rods in CRS reflects infection or colonization.¹

The detection of anaerobic bacteria is especially dependent on culture technique. Accordingly, reported rates of anaerobic bacteria in CRS patients vary significantly, ranging from 3 to 93%.^{9,13,14,16,17,21–23} The anaerobic bacteria isolated in positive studies have been predominantly *Prevotella*, *Fusobacterium*, and *Peptostreptococcus* species.^{14,17,18,21,24} Although the role of anaerobic bacteria in the pathogenesis of CRSwNP remains uncertain, some evidence suggests that anaerobic bacteria modulate disease severity; Finegold *et al.* found a direct correlation between sinonasal anaerobic bacterial counts and frequency of exacerbations in CRS patients.²¹

Biofilms in CRSwNP

The role of biofilms in the pathogenesis of CRSwNP has also generated significant interest. Biofilms arise when microorganisms adhere to surfaces such as sinonasal mucosa, interact with adjacent microbes, and together form an overlying protective extracellular matrix. Bacteria within biofilms are more resistant to host defenses and antibiotics^{25–28}—experiments suggest that biofilms can decrease bacterial susceptibility to antibiotics by 1000-fold.¹¹ Biofilms are also

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thought to be a source of recurrent infections *via* intermittent release of free-floating bacteria.²⁹

Reported rates of biofilms in CRS populations range from 28.6 to 100%,^{30–37} but these disparate results may be partially attributable to differing methods of identifying biofilms among studies. Research on biofilms specific to CRSwNP is very limited, but one small study of 12 CRSwNP patients found the prevalence of biofilms in CRSwNP to be 75%.³⁷ In comparison, biofilms have been largely absent in control subjects,^{34,35} although biofilms were detected in two (of five) control subjects in a study by Sanderson *et al.*³³ Biofilms in CRS patients have been associated with multiple bacterial species, including *P. aeruginosa*, *S. aureus*, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.^{28,30,31,33,36,38} Of note, the presence of biofilms in CRSwNP patients has been associated with persistent symptomatic disease after endoscopic sinus surgery.^{35,38} Thus, biofilms may modulate disease severity in at least a subset of CRSwNP patients, but their role in the pathogenesis of CRSwNP still is not clear.

The Superantigen Hypothesis

The superantigen (SAg) hypothesis suggests that noninvasive *S. aureus* in the nasal mucosa of CRS patients secretes SAg toxins that trigger local eosinophilic inflammation.^{39–41} Evidence for a SAg effect in CRSsNP patients is thus far lacking⁴¹; at most, SAg's may play a role in the pathogenesis of CRSwNP. CRSwNP patients appear to have a higher rate of nasal colonization with *S. aureus* compared with CRSsNP and control patients,⁴¹ as well as higher levels of nasal tissue SAg toxins,⁴⁰ local immunoglobulins (including IgE),^{39,42} SAg-specific IgE,⁴¹ eosinophils, and markers of eosinophilic inflammation.^{39–41} However, *S. aureus* and its effects do not appear to be universal to CRSwNP patients: the *S. aureus* colonization rate for CRSwNP is ~65%,⁴¹ the proportion of CRSwNP patients found to have SAg-specific IgE is ~50%,³⁹ and only about one-third of CRSwNP patients sampled in one study were found to have SAg-specific T-cell changes.⁴³ Thus, the literature suggests a possible role for SAg's in the pathogenesis of nasal polyps, but the SAg hypothesis can not account for all CRSwNP.

The Fungal Hypothesis

The fungal hypothesis proposes that CRS patients exhibit a unique T-cell-driven hypersensitivity to fungi that is not mediated by IgE,^{44–46} the immunoglobulin primarily responsible for atopic disease.⁴⁷ This hypothesis was derived from studies showing a high frequency of fungi and eosinophilic mucin in CRS patients,^{44,48} followed by experiments showing that peripheral blood mononuclear cells (PBMCs) and eosinophils of CRS patients reacted to *Alternaria* fungal extracts whereas cells from control subjects did not.⁴⁹ Despite these data, several important concerns remain regarding the fungal hypothesis. First, the suggestion of a T-cell-mediated hypersensitivity to fungi still has to be supported by mechanistic evidence for a T-cell receptor response to fungal antigens unique to CRS.⁴⁹ Second, it remains unclear whether the PBMCs in the aforementioned study reacted to *Alternaria* extract because of nonspecific protease effects of the *Alternaria* extract, rather than *via* an antigen-specific T-cell-mediated response. In either case, the amount of fungal extract applied in these studies may be higher than what occurs *in vivo*.⁴⁹ Third, CRS disease in other populations has not correlated with PBMC reactivity to *Alternaria* extract.⁵⁰ Finally, “proof-of-concept” studies evaluating the efficacy of antifungal therapy in both CRSwNP and CRSsNP patients have been largely negative.^{45,51–58} Taken altogether, the literature on the fungal hypothesis has not shown a clear role for fungi in the pathogenesis of CRSwNP. Fungi may modulate disease in a subset of CRSwNP patients; however, this potential subset of CRSwNP patients still is not well characterized.

ROLE OF T CELLS IN CRSwNP

Background on T-Helper Cells

Advances in the understanding of T-helper (T_H) cells have been followed by increased insight into the role of T_H cells in the pathogenesis of CRSwNP. Classically, T_H cells have been divided into T_{H1} and T_{H2} based on the cytokines they secrete. The hallmark of T_{H1} cells is their production of interferon (IFN)- γ . IFN- γ and other T_{H1} cytokines enhance defense against primarily intracellular microbes, in part by activating neutrophils and macrophages.⁵⁹ In contrast, T_{H2} cells are associated with eosinophilic inflammation,⁶⁰ and T_{H2} cell production of interleukin (IL)-4, IL-5, and IL-13 promotes helminth immunity but is also associated with atopy.⁶¹ This dichotomy of T_H cells has been amended in recent years with the identification of additional T-cell subsets, including T_{H17} and T-regulatory (T_{reg}) cells. T_{H17} cells characteristically produce IL-17 and promote host defense against extracellular pathogens^{61–64}; they have also been linked to autoimmune diseases including inflammatory bowel disease.⁶⁵ In contrast, T_{reg} cells maintain self-tolerance and inhibit autoimmunity.⁶¹ Of note, transforming growth factor (TGF)- β and IL-6 together promote T_{H17} cell differentiation, whereas TGF- β alone without IL-6 favors the differentiation of T_{reg} cells.⁶¹

T_H Profiles in CRSwNP

Although CRSsNP has been associated with elevated sinonasal levels of IFN- γ and thus a T_{H1} inflammatory profile,^{66,67} the preponderance of eosinophils and eosinophilic products found in multiple studies of nasal polyp tissue has implicated T_{H2}-mediated inflammation in the pathogenesis of CRSwNP.^{39,67–69} This is supported by evidence primarily from Europe of increased T_{H2} cytokines in nasal polyps including IL-5 and IL-13,^{66,67} as well as increased expression of the transcription factor GATA-3,⁶⁶ which regulates T_{H2} cytokine synthesis and is thus critical for T_{H2} differentiation.⁷⁰ Other studies suggest that eosinophilic inflammation in CRSwNP may be promoted by increased levels of IL-33 and/or thymic stromal lymphopoietin, which have been linked to other T_{H2} inflammatory diseases such as asthma and atopic dermatitis.^{71–77} Additionally, a relative insensitivity to suppressants of T_{H2}-mediated inflammation such as hepatocyte growth factor may play a role in the pathogenesis of CRSwNP.⁷⁸

A caveat to these distinct T_H profiles found in CRSwNP versus CRSsNP is that the anatomic location of sinonasal tissue studied from these two groups has differed: sinonasal CRSsNP tissue has been compared with nasal polyps, leaving open the possibility that differential T_H profiles could be caused by anatomic variation.^{66,67} Furthermore, the finding of eosinophilia in CRSwNP has not been universal.^{67,68} Experiments using polyp tissue from CRSwNP patients in China have identified a predominantly T_{H1} and T_{H17} pattern,⁶⁸ and nasal polyps in cystic fibrosis patients are also predominantly neutrophilic.⁶⁷ The heterogeneous T_H inflammatory profiles found in CRSwNP suggest that a variety of pathogenetic mechanisms may result in the clinical phenotype of CRSwNP.

T_{reg} Cells in CRSwNP

Increasing evidence points to the importance of T_{reg} cells in preventing autoimmunity and atopy.^{61,79} T_{reg} development from T_H cells inhibits T_{H17} differentiation,⁸⁰ and T_{reg} cells regulate T_{H1} and T_{H2} immune responses.^{79,81} Expression of the transcription factor forkhead box P3 (FOXP3) is characteristic of T_{reg} cells,⁸⁰ and studies have shown decreased FOXP3 expression in CRSwNP patients from both Europe and China.^{66,68,82} Decreased FOXP3 in CRSwNP tissue correlated with increased expression of characteristic T_{H1} and T_{H2} transcription factors (T-box transcription factor and GATA-3, respectively),⁶⁶ suggesting that an impairment in T_{reg} cells may contribute to the inflammation in CRSwNP. Other investigators have found evidence of increased IL-6 but impaired IL-6 signaling in CRSwNP

sinonasal tissue, leading to the hypothesis that increased IL-6 may contribute to the pathogenesis of CRSwNP *via* inhibition of T_{reg} function and/or recruitment of T_H inflammatory cells.⁸³ In summary, there is increasing evidence implicating T_{reg} cell dysfunction in the pathogenesis of CRSwNP.

ROLE OF INNATE IMMUNITY IN CRSwNP

The aforementioned literature on the possible role of immune dysregulation in CRSwNP has focused primarily on adaptive immunity, which is exquisitely pathogen specific and includes B and T cells.⁸⁴ However, defects in innate immunity may also contribute to the pathogenesis of CRSwNP. Simply put, innate immunity includes the epithelial barrier and molecules that are directed against shared microbial patterns rather than pathogen-specific antigens.^{46,84} Studies of innate immunity in CRSwNP have focused primarily on Toll-like receptors (TLRs), B-cell activating factor of the TNF family, and epithelial cell function.

TLRs in CRSwNP

TLRs are pattern-recognition receptors that recognize pathogen-associated molecular patterns and are found in various tissues, including sinonasal mucosa.^{46,84–86} Studies suggest that TLR2 and TLR9 may play a role in the pathogenesis and/or severity of CRSwNP. TLR2 recognizes bacteria and fungi,^{46,87} and TLR9 recognizes unmethylated cytosine-phosphate-guanine motifs characteristic of bacterial DNA.^{87–89} One study restricted to CRSwNP patients showed lower TLR9 expression in CRSwNP sinonasal tissue compared with controls.⁸⁸ In another study, expression of TLR2 was found to be higher in CRS patients (CRSwNP and CRSsNP) compared with controls, but the authors did not examine CRSwNP patients separately.⁹⁰ The latter study also found that levels of TLR2 and TLR9 expression correlated with CRS disease severity: CRS patients who were more refractory to medical and surgical management had significantly lower expression of TLR2 and TLR9 in sinonasal tissue.⁸⁸ In short, there is some evidence to suggest a correlation between TLR expression and CRSwNP, but that relationship still is not entirely clear.

B-Cell Activating Factor of the TNF Family and CRSwNP

B-cell activating factor of the TNF family (BAFF; also known as BLyS, TNFSF13B, TALL-1, and THANK) is a protein that affects B-cell survival, proliferation, and antibody production.^{91–93} Recent experiments suggest that BAFF may contribute to the pathogenesis of CRSwNP.⁹⁴ Kato *et al.* found that BAFF is produced by sinonasal mucosal epithelium, as well as by cells in the sinonasal submucosa that still have to be identified.⁹⁴ In the same study, significantly higher levels of BAFF were found in sinonasal tissue from CRSwNP patients compared with CRSsNP and control subjects. BAFF expression significantly correlated with higher levels of B-cell markers, including transmembrane activator and CAML interactor, a B-cell receptor that mediates B-cell production of IgA.⁹⁴ IgA has been associated with eosinophilic inflammation independent of IgE.^{95–98} Taken together, this evidence suggests that overproduction of BAFF in CRSwNP may lead to B-cell proliferation and IgA synthesis, which in turn may contribute to the eosinophilic infiltrate often found in nasal polyps (as mentioned previously).^{39,67–69,94} Recent evidence also suggests that the chemokines B-cell attracting chemokine 1 (BCA-1, also known as CXCL13 and BLC) and stromal cell-derived factor 1 α (SDF-1, also known as CXCL12) may also modulate the B-cell response in CRSwNP.⁹⁹ However, the mechanism underlying overproduction of BAFF, BCA-1, and SDF-1 in CRSwNP still is to be elucidated.

Epithelial Cell Function and CRSwNP

Epithelial cell dysfunction has long been associated with the pathogenesis of CRS, *e.g.*, the high prevalence of CRS in patients with

primary ciliary dyskinesia is well known.^{100–102} However, recent studies have highlighted the multiplicity of mechanisms by which epithelial cell dysfunction may underlie the development of CRS. Respiratory epithelial cells are important in innate immunity not only because they form a barrier to pathogen entry and mediate mucociliary clearance of potential pathogens, but also because they produce antimicrobial agents such as S100A7 (psoriasin) and S100A8/A9 (calprotectin).^{103–105} S100A7 is active against *E. coli* and acts by permeabilizing bacterial membranes^{103,104,106}; S100A8/A9 has both antibacterial and antifungal properties.^{105,107} Significantly lower levels of S100A7 and S100A8/A9 expression have been found in sinonasal epithelial cells from CRSwNP and CRSsNP patients compared with controls.^{108,109} Protein levels of S100A7 and S100A8/A9 found in nasal lavage are also significantly lower in CRSwNP and CRSsNP patients compared with controls.¹⁰⁹ Lower levels of antimicrobial proteins in CRSwNP sinonasal epithelium may increase susceptibility to colonization and/or invasion by pathogens, leading to an increased inflammatory response.¹⁰⁹ Thus, a defect in epithelial cell synthesis of antimicrobial products may play a role in the pathogenesis of CRSwNP.

TISSUE REMODELING AND CRSwNP

The foregoing discussion has focused on the possible role of pathogens and altered immunity in the pathogenesis of CRSwNP, but reports of potentially pathological tissue remodeling in CRSwNP also warrant mention. Studies have found significantly less collagen and less TGF- β expression and TGF- β signaling in CRSwNP sinonasal tissue compared with CRSsNP.^{82,110,111} TGF- β has multiple effector functions, including modulating T_{reg}/T_{H17} differentiation (as discussed previously) and regulating extracellular matrix synthesis and remodeling.¹¹² Thus, it has been suggested that low levels of TGF- β in CRSwNP contribute to decreased tissue repair and collagen deposition, which in turn result in edema formation and nasal polyposis.¹¹⁰ In contrast, increased levels of TGF- β and collagen found in CRSsNP may be responsible for excessive tissue repair and fibrosis.¹¹⁰ This hypothesis is supported by some evidence that CRSwNP patients differ significantly from controls in the concentration of matrix metalloproteinases (MMPs; which act on extracellular matrix components) and tissue inhibitors of MMPs (TIMPs) found in sinonasal tissue.^{82,113} TGF- β may affect sinonasal levels of MMPs and TIMPs and, ultimately, effect nasal polyposis; a recent *ex vivo* study has also suggested that *S. aureus* may also promote polyposis by altering the MMP/TIMP milieu.¹¹⁴ Further studies are needed to delineate these two potential pathways of polyp generation.

ARACHIDONIC ACID METABOLISM AND CRSwNP

Approximately 15% of patients with CRSwNP have coexistent asthma and aspirin sensitivity, also known as AERD, aspirin triad, or Samter's triad.¹¹⁵ This syndrome is characterized by severe nasal and respiratory symptoms after ingestion of aspirin or other nonsteroidal anti-inflammatory drug, and the nasal polyps of AERD patients are characterized by significant eosinophilia.¹¹⁶ Experiments have suggested that the pathogenesis of nasal polyposis in AERD may be multifactorial,¹¹⁷ but the majority of literature on the pathophysiology of AERD focuses on alterations in arachidonic acid metabolism. Compared with asthmatic patients who tolerate aspirin, AERD patients before nonsteroidal anti-inflammatory drug ingestion already have higher respiratory tract levels of cyclooxygenase and 5-lipoxygenase products such as leukotriene E₄ (LTE₄) and thromboxane B₂,¹¹⁸ as well as increased respiratory tract expression of the cysteinyl leukotriene 1 receptor and leukotriene C₄ synthase (LTC₄ synthase), an enzyme important in the synthesis of cysteinyl leukotrienes.^{116,119} Aspirin ingestion in AERD patients not only induces upper and lower respiratory symptoms, but it also increases leukotriene C₄ (LTC₄) levels in nasal and bronchial mucus and increases expression of cysteinyl leukotriene receptors in the respiratory tract.^{116,120} Con-

versely, aspirin desensitization reduces LTC4 levels in nasal secretions, lowers the expression of cysteinyl leukotriene receptors in the respiratory tract, and decreases polyp recurrence in AERD patients.^{119,121} For these reasons, aberrant arachidonic acid metabolism is implicated in the pathogenesis of CRSwNP in AERD patients. Studies suggest that this pathway may also be relevant to CRSwNP patients who are tolerant of aspirin,^{122,123} but further research exploring this potential relationship is needed.

CONCLUSION

In conclusion, CRS is a common disease, and emerging evidence suggests that the pathogenesis of CRSwNP may differ from CRSsNP. Evidence suggests that altered innate immunity, adaptive immunity, tissue remodeling, aberrant arachidonic acid metabolism and/or effects of microorganisms may play a role in the development of CRSwNP. Additional research is needed to elucidate these pathways and to determine their relative importance in the pathogenesis of CRSwNP.

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