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REVIEW ARTICLE

The sinonasal microbiome, host defense peptides, and cancer risk: Decoding the immune system's dilemma in chronic rhinosinusitis

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Abstract

Chronic rhinosinusitis (CRS) is a prevalent and debilitating condition characterized by persistent inflammation of the sinonasal mucosa. Despite advances in understanding its pathophysiology, the role of microbial communities and their interactions with the host immune system remains poorly understood. This review aims to elucidate the complex interplay between microbial dysbiosis, host immune responses, the dysregulated, cancer-like behavior of inflamed sinus tissue, and the production of antimicrobial peptides (AMPs) and lipids in CRS. A systematic literature review was conducted across databases such as PubMed, Scopus, and Web of Science. Keywords included "chronic rhinosinusitis,""microbial interactions,""antimicrobial peptides,""antimicrobial lipids," and "immune system." Studies published between 2020 and 2025 were included, focusing on microbial–immune interactions, AMPs, and lipids in CRS. Data were synthesized to identify key mechanisms and therapeutic implications. Microbial dysbiosis in CRS is associated with altered immune responses and impaired production of AMPs and lipids. Studies demonstrate that microbial interactions can either exacerbate or mitigate inflammation, depending on the balance between pathogenic and commensal species. Immune system dysregulation, particularly in T-cell responses and cytokine production, further exacerbates chronic inflammation. Emerging therapies, such as probiotics and AMP-based treatments, show promise in restoring microbial-immune balance. Future research should focus on developing targeted therapies that restore microbial balance and enhance innate immune defenses. Understanding the role of microbial interactions in CRS offers new avenues for personalized treatment strategies, potentially improving outcomes for patients with this challenging condition.

Keywords: Chronic rhinosinusitis; Microbial interactions; Antimicrobial peptides; Antimicrobial lipids; Immune system

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1. Introduction

Chronic rhinosinusitis (CRS) is a prevalent and debilitating inflammatory disease of the paranasal sinuses, affecting a significant portion of the global population and imposing a substantial burden on healthcare systems and patient quality of life. Clinically characterized by symptoms such as nasal obstruction, rhinorrhea, facial

pain, and loss of smell persisting for more than 12 weeks, CRS is a heterogeneous disorder with diverse underlying pathophysiologies. While historically viewed as a simple consequence of bacterial infection or anatomical obstruction, our understanding of CRS has evolved to recognize it as a complex, multifactorial disease driven by a dysfunctional interplay between environmental factors, the sinus microbiome, and the host's immune response. Despite advances in medical and surgical management, a considerable number of patients remain refractory to treatment, underscoring the critical need to dissect the intricate molecular and cellular mechanisms that perpetuate chronic inflammation.[1]

The immune response in CRS is often persistent and self-perpetuating, sharing surprising similarities with the immune evasion strategies observed in cancer.[2] In this review, we explore the paradigm shift from infection to dysbiosis, examining how an imbalance in the sinus microbial community, rather than a single pathogen, contributes to a pro-inflammatory environment and disrupts mucosal homeostasis. The role of the host immune system is paramount. This review examines dysregulated immune responses in CRS, focusing on the aberrant activation of innate and adaptive immunity, the role of specific T-helper (Th) cell polarizations (e.g., Th1, Th2, and Th17), and the resulting cytokine milieu that defines various CRS endotypes.

A compelling and emerging concept in CRS is the observation of cancer-like characteristics in the chronically inflamed sinus tissue. We examine cancer-like features, including tissue remodeling, epithelial-to-mesenchymal transition, enhanced angiogenesis, and resistance to apoptosis, which collectively contribute to the recalcitrant, hyperplastic nature of the disease. The sinus epithelium is not a passive barrier but an active defender. We analyze the synthesis and function of key host-derived defense molecules, including antimicrobial peptides (AMPs; e.g., defensins and cathelicidins) and lipid mediators (e.g., eicosanoids and specialized pro-resolving mediators). The imbalance between protective and inflammatory mediators in these classes is a critical factor in determining disease chronicity and resolution.

By integrating these facets, this review seeks to offer a holistic and mechanistic perspective on CRS.[3] The epidemiology of CRS underscores its profound public health impact. It is estimated to affect 5–12% of the general population in developed countries, leading to millions of physician visits and a vast number of prescribed medications annually. Beyond direct healthcare costs, indirect costs from absenteeism, presenteeism, and reduced productivity are immense. However, the actual burden of CRS is perhaps most acutely felt in its devastating effect on patients' quality of life. Studies consistently show that the impact of CRS on physical functions, social functioning, and mental health is comparable to, or even exceeds, that of other chronic conditions, such as chronic obstructive pulmonary disease, congestive heart failure, and chronic back pain. The persistent nature of symptoms, particularly the loss of smell and chronic fatigue, leads to social isolation, nutritional issues, and a significant increase in the prevalence of depression and anxiety, creating a heavy personal and societal toll.[4-6]

The pathophysiology of CRS is complex and multifactorial, traditionally conceptualized as an interplay between host and environmental factors. The "unified airway" model links CRS closely with other inflammatory conditions, such as asthma and allergic rhinitis, suggesting shared pathogenic mechanisms. Central to the development of CRS is the disruption of the sinonasal homeostatic ecosystem. This involves a dysfunctional epithelial barrier, an aberrant immune response to both inhaled pathogens and environmental agents, and dysregulation of the local inflammatory milieu. Historically, research focused on the role of bacterial infection; however, the contemporary understanding has evolved to recognize that persistent inflammation, rather than active infection, is the cornerstone of the disease. This inflammation is sustained by a complex network of innate and adaptive immune cells, culminating in the characteristic tissue remodeling—including edema, fibrosis, polyp formation, and basement membrane thickening—observed in CRS patients.[7-10]

Current concepts posit that disruption of the homeostatic balance between the host and its microbial residents, known as dysbiosis, is a critical driver of the persistent inflammation observed in CRS. This dysbiosis is characterized not necessarily by the presence of a single pathogenic species, but by a shift in the overall microbial community structure, often with a loss of beneficial commensals and an expansion of pro-inflammatory pathobionts.[11] Concurrently, the host's immune response in CRS is marked by distinct endotypes, most notably the Th2-skewed inflammation seen in patients with comorbid asthma and nasal polyps and the more Th1-/Th17-dominated profile in those without polyps.[12] The central, yet incompletely resolved, question is how these specific immune responses and the sinus microbial ecosystem interact reciprocally to initiate and perpetuate the disease cycle.

Nasal secretions, often collected through lavage, swabbing, or an absorbent matrix, provide a unique and non-invasive window into the host–microbe interface. These secretions are a rich source of both microbial DNA,

enabling profiling of the entire microbial community through 16S ribosomal RNA (rRNA) gene sequencing, and a plethora of host-derived immune factors, including cytokines, immunoglobulins, AMPs, and proteases.[13] The simultaneous analysis of these two components from the same sample offers an unprecedented opportunity to move beyond correlation toward a mechanistic understanding of CRS pathogenesis. Therefore, the primary objective of this review is to synthesize and critically evaluate the existing body of literature concerning the collection and examination of nasal secretions from CRS patients.[14,15]

In CRS, however, these defense mechanisms are often compromised. Alterations in the expression and function of AMPs and antimicrobial lipids have been observed, leading to impaired microbial clearance and chronic inflammation. In addition, the interplay between the microbiota and the immune system is disrupted, creating a vicious cycle of microbial dysbiosis, immune dysregulation, and tissue damage. Understanding these interactions is crucial for developing targeted therapies that restore microbial balance and enhance host defense mechanisms.[16-19] This review delves into the intricate molecular and cellular mechanisms that underpin the inflammatory state in CRS. We aim to move beyond a superficial description and provide detailed insights into several pertinent and interconnected aspects of the disease's pathogenesis. Specifically, we explore the critical role of microbial dysbiosis, where an imbalance in the sinonasal microbiome between beneficial and pathobiont organisms disrupts immune homeostasis and fuels inflammation. We then examine the consequent host immune reactivity, dissecting the dominant endotypes—namely, the type 2 inflammatory response, often associated with nasal polyps and eosinophilia, and the non-type 2 pathways. Furthermore, we discuss the emerging concept of cancer-like behavior in inflamed tissue, where processes such as epithelial-to-mesenchymal transition, sustained proliferation, and resistance to apoptosis contribute to polyp growth and recalcitrant disease. Finally, we synthesize the current understanding of the synthesis and function of AMPs and lipids in the sinonasal mucosa, highlighting how their deficiency or dysfunction impairs the first line of defense and perpetuates the cycle of inflammation and dysbiosis. By integrating these key facets, this review seeks to clarify the pathogenic landscape of CRS and illuminate potential avenues for novel, targeted therapeutic strategies.

2. Literature review methodology

A comprehensive literature search was performed across electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search terms included combinations of the following keywords: "antimicrobial peptides," "immune system dynamics," "chronic rhinosinusitis," "microbial interactions," "host-pathogen interactions," "biofilms," "innate immunity," and "therapeutic applications." Articles published in English from 2020 to 2025 were included. Studies focusing on the role of AMPs in CRS, their interaction with microbial communities, and their impact on immune system dynamics were prioritized. Both *in vitro* and *in vivo* studies, as well as clinical trials, were considered. Duplicate articles were removed, and the remaining studies were screened based on titles and abstracts. Full-text articles were reviewed for relevance, and references from selected articles were cross-checked to identify additional studies (Table 1).

3. Results

3.1. Understanding CRS

CRS is broadly categorized into two subtypes: CRS with nasal polyps and CRS without nasal polyps. Symptoms include nasal congestion, facial pain, hyposmia (reduced sense of smell), and purulent nasal discharge. Traditional treatment approaches involve corticosteroids, saline irrigation, and antibiotics targeting common pathogens, such as *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*. However, a subset of patients fails to respond to conventional therapies, prompting clinicians to explore alternative etiologies, including atypical bacterial infections.[36,37]

3.2. The sinus microbiome in health and disease

The sinonasal cavity harbors a diverse community of microorganisms, collectively known as the sinus microbiome. In healthy individuals, this microbiome is relatively stable and consists of commensal bacteria that coexist harmoniously with the host, contributing to immune regulation and protection against pathogens. However, in CRS, this microbial balance is disrupted, leading to dysbiosis, a state of microbial imbalance that promotes inflammation and disease.[14] Studies using advanced sequencing technologies, such as 16S rRNA gene sequencing, have revealed distinct differences in the sinus microbiome of CRS patients compared to healthy controls. CRS is often associated with a reduction in microbial diversity and an overgrowth of pathogenic or opportunistic bacteria, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *H. influenzae*. These pathogens can form biofilms, which are structured communities of bacteria encased in a protective extracellular matrix. Biofilms are highly resistant to antibiotics and immune clearance, contributing to the chronic and recurrent nature of CRS.[38,39]

Table 1. Integration of AMPs and immune system dynamics in CRS, with a focus on microbial interactions

Categories	Hypothesis	Results	Example quotes	References
Immune modulation by AMPs	AMPs play a critical role in modulating immune responses in CRS.	AMPs such as defensins and cathelicidins regulate immune cell activity.	"Human neutrophil α-defensin HNP1 interacts with bacterial cell wall components to promote biofilm formation by *S. aureus*."[22(p1)]	20-22
Microbial dysbiosis and AMPs	Dysbiosis in CRS correlates with AMP dysregulation.	Imbalance in microbial communities reduces AMP efficacy.	"*S. aureus* biofilms suppress AMP production in CRS patients."[7(p4)]	7,23,24
Advances in AMP research	Advances in AMP research improve therapeutic strategies.	Advanced techniques in AMP synthesis and delivery.	"Advanced in peptide engineering enhances AMP stability and bioavailability."[26(p1)]	7,25
Immune system dynamics	Immune system dynamics are altered by microbial–AMP interactions.	AMPs influence cytokine profiles and T-cell responses.	"Cytokine family members have diverse biological functions, promoting protective immunity against many pathogens but also driving inflammatory pathology."[7(p4)]	7,26
Therapeutic applications of AMPs	AMP-based therapies show promise in CRS treatment.	Clinical trials on synthetic AMPs for CRS.	"Synthetic AMPs reduce bacterial load and inflammation in CRS patients."[30(p13)]	27,28
Microbial resistance mechanisms	Microbial resistance to AMPs is a growing concern.	Bacteria evolve resistance to AMPs through genetic mutations.	"*Pseudomonas aeruginosa* develops resistance by altering membrane composition."[30(p3)]	28-30
Host–microbiota interactions	AMPs interact with host microbiota to maintain homeostasis.	AMPs shape microbial communities in the sinonasal cavity.	"AMPs promote beneficial commensals while suppressing pathogens in CRS."[31(p3)]	30,31
Pathogen immune evasion	Immune evasion by pathogens reduces AMP efficacy.	Pathogens secrete proteases to degrade AMPs.	"*S. aureus* secretes proteases that cleave human β-defensins, evading immune attack."[35(p1)]	32-35

Abbreviations: AMPs: Antimicrobial peptides; CRS: Chronic rhinosinusitis; *S. aureus*: *Staphylococcus aureus*.

3.3. The role of microbial interactions in CRS

CRS is a persistent inflammatory condition of the paranasal sinuses and nasal mucosa, lasting for 12 weeks or longer. It is a common and debilitating condition that significantly impacts patients' quality of life, causing symptoms such as nasal congestion, facial pain, reduced sense of smell, and fatigue. While the exact etiology of CRS remains incompletely understood, emerging research highlights the critical role of microbial interactions in its pathogenesis. The complex interplay between bacteria, fungi, viruses, and the host immune system contributes to the chronicity and heterogeneity of CRS.[11,40]

3.4. The role of bacteria in CRS

Coneventionally, CRS has been associated with bacterial infections, particularly those caused by *S. aureus*, *P. aeruginosa*, and *H. influenzae*. However, the presence of these bacteria in sinus cultures does not always correlate with disease severity or treatment outcomes. This discrepancy has led researchers to explore alternative mechanisms, including the possibility that certain bacteria may evade the immune system and antibiotic therapy by residing inside host cells. Microbial interactions play a pivotal role in the development and persistence of CRS. These interactions occur not only between different microbial species but also between microbes and the host immune system.[41]

3.5. Bacterial involvement in CRS pathogenesis

In healthy individuals, the sinuses are sterile or colonized by a balanced microbiome that does not cause harm. However, in CRS, this balance is disrupted, leading to bacterial overgrowth or the presence of pathogenic species. Common bacterial pathogens associated with CRS include *S. aureus*, *P. aeruginosa*, *H. influenzae*, and *S. pneumonia*.[1,42]

3.6. Intracellular bacteria in patients with CRS: A hidden culprit?

CRS is a common and debilitating condition characterized by inflammation of the paranasal sinuses lasting for 12 weeks or longer. Despite its prevalence, the underlying causes of CRS remain poorly understood, with factors such as allergies, environmental triggers, and microbial infections playing complex roles. In recent years, emerging research has shed light on the potential involvement of intracellular bacteria in the pathogenesis of CRS, raising questions about their role in disease persistence and treatment resistance.[1,43]

3.7. Atypical bacterial infections in CRS

Atypical bacteria are microorganisms that do not respond to standard laboratory culturing techniques and often require specialized methods for detection. These pathogens are typically intracellular or have unique

growth requirements, making them difficult to identify using traditional diagnostic approaches. In the context of CRS, the most commonly implicated atypical bacteria include *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *S. aureus* (small-colony variants). Atypical bacteria can induce a dysregulated immune response, leading to chronic inflammation. For example, C. pneumoniae and M. pneumoniae have been shown to stimulate the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which perpetuate sinus inflammation and tissue remodeling.[44,45]

3.7.1. Pathogen–pathogen interactions

In CRS, pathogenic bacteria often interact synergistically, enhancing each other's virulence. For example, *S. aureus* and *P. aeruginosa* are frequently co-isolated in CRS patients. These bacteria can engage in cross-communication through quorum sensing, a process that allows them to coordinate gene expression and biofilm formation. In addition, *S. aureus* can produce toxins that damage the epithelial barrier, facilitating the invasion of other pathogens such as *P. aeruginosa*.

3.7.2. Bacterial–fungal interactions

Fungi, particularly *Aspergillus* and *Candida* species, are also implicated in CRS, especially in cases of fungal ball or allergic fungal rhinosinusitis. Bacterial–fungal interactions can exacerbate inflammation and tissue damage. For example, *S. aureus* and *Candida albicans* can form mixed biofilms, which are more resistant to treatment than single-species biofilms. Furthermore, fungal proteases can degrade host tissues, creating a favorable environment for bacterial colonization.[46]

3.7.3. Viral–bacterial interactions

Viral infections, such as those caused by rhinoviruses or influenza viruses, can predispose individuals to bacterial superinfections in the sinuses. Viruses can impair mucociliary clearance, disrupt the epithelial barrier, and modulate the immune response, creating an environment conducive to bacterial colonization and biofilm formation. Viruses, particularly those responsible for upper respiratory tract infections, are increasingly recognized as key contributors to the initial inflammatory cascade that may lead to the development of CRS. Respiratory viruses, such as rhinovirus, influenza virus, respiratory syncytial virus, and adenovirus, are common culprits in acute viral rhinosinusitis. In most individuals, these infections are self-limiting and resolve without complications. However, in susceptible individuals, viral infections can trigger a dysregulated immune response, leading to persistent inflammation and mucosal damage. This aberrant response may be influenced by host factors, including genetic predisposition, environmental exposures, and underlying immune dysfunction.[47]

3.7.4. Microbe–host interactions

The host immune response to microbial colonization is a critical factor in CRS pathogenesis. In some patients, an exaggerated immune response to commensal or pathogenic microbes leads to persistent inflammation. For example, *S. aureus* produces superantigens that can trigger a robust T-cell response, contributing to tissue damage and chronic inflammation. In addition, dysbiosis can alter the production of AMPs and cytokines, further disrupting immune homeostasis.[48-50]

3.8. The overlooked virosphere: Viral influence on sinonasal immunity and microbial ecology

A central finding of this systematic review is the pronounced bias within the existing literature toward characterizing the bacterial component of the sinonasal microbiome. While these studies have been invaluable for establishing a baseline understanding of microbial communities in health and diseases such as CRS, the viral constituent of the virome remains largely unexplored. The majority of identified studies utilized 16S rRNA gene sequencing, a technique inherently blind to viral presence. Consequently, the role of viruses in shaping the sinonasal mucosal environment, modulating host defense mechanisms, and interacting with bacterial residents is critically under-represented. This creates a pro-inflammatory environment rich in damage-associated molecular patterns and depleted resources, which can paradoxically favor colonization by opportunistic pathogens such as *S. aureus* and *P. aeruginosa*.[51]

Beyond acute epithelial damage, viruses exert a more subtle and persistent influence on the production of key host-defense peptides (HDPs), a critical component of the innate immune system. AMPs such as β-defensins, S100 proteins (e.g., calprotectin), and cathelicidin (LL-37) are vital for maintaining microbial homeostasis on mucosal surfaces. Evidence suggests that viral infections can dysregulate the expression of these peptides. For example, rhinovirus infection has been shown to downregulate the expression of specific β-defensins in airway epithelial cells, potentially creating a permissive environment for secondary bacterial infection. Conversely, some viruses may induce certain AMPs as part of the generalized inflammatory response; however, the net effect often appears to be a failure of targeted, effective antimicrobial defense, leading to a state of immune dysregulation that benefits other members of the microbiome.[52]

Perhaps the most significant, yet least studied, aspect of sinonasal virology is the impact of bacteriophages—viruses that specifically infect bacteria. Bacteriophages are likely the most abundant biological entities in the sinonasal cavity and are pivotal players in bacterial ecology and evolution. Through predator–prey dynamics, they can directly modulate bacterial population densities and diversity. More importantly, phages drive bacterial evolution through lysogenic conversion, where the integration of phage DNA into the bacterial genome can confer new pathogenic traits. A canonical example is the conversion of a benign *S. aureus* strain into a toxigenic one through the acquisition of a phage encoding the Panton–Valentine leukocidin toxin.

In the context of CRS, phage-mediated transfer of genes encoding other virulence factors, biofilm-enhancing proteins, or antibiotic resistance determinants could fundamentally alter the disease's trajectory and chronicity. The interaction among viruses, HDPs, and bacteria is likely a complex, tripartite relationship. The host's production of AMPs in response to a viral threat may not only be ineffective against the virus but also apply selective pressure on the bacterial community, enriching for resistant species. Simultaneously, bacteria can modulate AMP expression, for example, *S. aureus* can upregulate its own biofilm formation in response to LL-37, enhancing its resilience. Bacteriophages, in turn, may exploit this stressed bacterial state for their own replication. Furthermore, some evidence suggests that certain HDPs can directly influence phage activity, either by neutralizing viral particles or by inducing the lytic cycle in lysogenic bacteria, effectively triggering the destruction of their bacterial host. This intricate web of interactions represents a significant gap in our current knowledge of sinonasal pathophysiology.

3.9. Implications for diagnosis and treatment

Understanding the role of microbial interactions in CRS has important implications for its diagnosis and treatment. Traditional culture-based methods often fail to capture the full complexity of the sinus microbiome, highlighting the need for molecular techniques such as metagenomic sequencing to characterize microbial communities and their functional potential. Personalized approaches that consider the unique microbial and immune profiles of individual patients may improve outcomes.[53-55] Current treatment strategies for CRS include antibiotics, corticosteroids, and surgery. However, these approaches often provide only temporary relief, as they do not address the underlying microbial dysbiosis and biofilm formation. Emerging therapies targeting microbial interactions, such as quorum-sensing inhibitors, probiotics, and bacteriophages, hold promise for restoring microbial balance and preventing recurrence. In addition, modulating the host immune response through biologics or immunotherapies may help break the cycle of chronic inflammation.[56,57]

3.10. The sinonasal microbiome: From initial homeostasis to pathologic dysregulation

A consistent theme emerging from the reviewed literature is the association between an altered sinonasal microbiome and a spectrum of chronic inflammatory diseases, most notably CRS. The included studies extensively cited the downstream consequences of microbial dysbiosis, effectively framing the microbiome as a central player in the effector phase of immune dysregulation. These downstream aspects include the breakdown of epithelial barrier integrity through the dysregulation of tight junction proteins; the sustained recruitment and activation of neutrophils, lymphocytes, and other innate immune cells; and the polarization of the adaptive immune response toward pathogenic Th2 or Th17 profiles, characterized by the production of cytokines such as IL-4, IL-5, IL-13, and IL-17.

Furthermore, several studies highlighted the role of dysbiotic communities in fostering a pro-inflammatory milieu through the production of specific virulence factors, toxins, and metabolites that directly damage host tissue and perpetuate a cycle of inflammation and microbial perturbation. While this body of evidence robustly describes the consequences of an established dysbiotic state, the early-stage triggering mechanisms that initiate the shift from a homeostatic to a dysbiotic microbiome remain a critical gap. To complete this model, we propose a framework that incorporates these initiating events, which can be broadly categorized into host-derived and environment-derived triggers.

3.11. Priming and disruption: The initiation of dysbiosis

The initial breach in sinonasal homeostasis potentially begins with an event that disrupts the delicate host–microbe interface. Key early triggering mechanisms include:

- Viral insult: A primary instigator is an acute viral upper respiratory infection (e.g., rhinovirus, influenza virus, and respiratory syncytial virus). These viruses do not merely cause transient inflammation; they can directly damage the ciliated respiratory epithelium, leading to sloughing of the protective mucus layer and exposing underlying receptors. This "hit-and-run" event creates a window of vulnerability by transiently suppressing innate immune responses and liberating host nutrients, thereby facilitating the initial colonization and overgrowth of opportunistic pathobionts residing within the community

- Failure of microbial competition: The early loss of key commensal species, particularly those producing bacteriocins or other antimicrobial compounds, can remove a critical ecological check on potential pathobionts such as *S. aureus* and *P. aeruginosa*. The depletion of these beneficial competitors, potentially through the indiscriminate use of antibiotics or the mechanisms above, creates a vacant niche that is rapidly filled by more inflammatory species.

3.12. Antibiotic resistance in CRS

The overuse and misuse of antibiotics in treating CRS have led to the emergence of antibiotic-resistant bacterial strains. *S. aureus*, particularly methicillin-resistant *S. aureus*, is a significant concern in CRS due to its resistance to multiple antibiotics. This resistance complicates treatment and often necessitates the use of more potent, more toxic antibiotics, which can have significant side effects.[49,58]

3.13. Biofilm formation and chronicity

One of the most significant challenges in treating CRS is the ability of bacteria to form biofilms. Biofilms are structured communities of bacteria encased in a self-produced extracellular matrix that adheres to the sinonasal mucosa. These biofilms are highly resistant to antibiotics and the host immune response, making them a key factor in the chronicity of CRS.[40,59,60]

4. Future directions and recommendations for empirical validation

The conceptual framework and literature synthesis presented in this paper provide a compelling model for understanding the complex interplay between microbial dysbiosis and immune dysregulation in CRS. The study has adeptly synthesized current literature to propose a plausible pathogenic cascade, identifying key microbial players and putative immune pathways. However, to transition from a compelling theoretical model to a foundational pillar of clinical understanding, the empirical rigor and persuasive capacity of this work must be bolstered through direct experimental or clinical validation.

A primary and highly feasible recommendation is to conduct controlled studies using well-characterized patient samples. While the review expertly extrapolates from existing studies, direct evidence generated from a dedicated cohort would powerfully substantiate its central thesis. A critical step in this direction would be the systematic collection and examination of nasal secretions or sinonasal tissue from CRS patients, stratified by phenotype (e.g., with or without nasal polyps) and endotype (e.g., Th2-high vs. Th2-low). The integration of these two datasets, microbiome and immunome, through advanced statistical modeling would be instrumental in verifying the theoretical analysis. For example, such an approach could directly test whether a high *S. aureus* burden is indeed correlated with elevated IL-5 and immunoglobulin E levels in the Th2-high subgroup, or whether a depletion of commensal *Corynebacterium* species is linked to a deficit in specific antimicrobial defenses. This methodology moves beyond correlation to provide a more mechanistic understanding of host–microbe interactions within the sinonasal niche.

4.1. The interplay between antimicrobial agents and innate immunity in CRS

The relationship between antimicrobial agents and host innate immunity in CRS is complex and bidirectional. On one hand, antimicrobial agents can modulate the immune response by reducing microbial load and biofilm formation, thereby alleviating inflammation. On the other hand, the immune system influences the efficacy of antimicrobial therapies by shaping the microbial environment and determining the extent of inflammation. For example, the use of macrolides in CRS has been shown to downregulate pro-inflammatory cytokines and enhance epithelial repair, highlighting the immunomodulatory properties of specific antimicrobial agents. Conversely, the innate immune system's ability to recognize and respond to pathogens can be compromised in CRS, leading to recurrent infections and the need for prolonged antimicrobial therapy.[61-63]

4.2. Host innate immunity in CRS

The innate immune system serves as the first line of defense against microbial invaders and is intricately involved in the pathogenesis of CRS. The sinonasal epithelium is equipped with physical barriers, such as mucociliary clearance, and chemical defenses, including AMPs such as defensins and cathelicidins. These components work in concert to prevent microbial colonization and invasion. In CRS, however, dysregulation of innate immunity is frequently observed. Pattern recognition receptors, such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), detect pathogen-associated molecular patterns on microbes and initiate immune responses. In CRS patients, aberrant signaling through these receptors can lead to excessive production of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, contributing to chronic inflammation. In addition, defects in epithelial barrier function and impaired mucociliary clearance further exacerbate the disease by allowing persistent microbial colonization.[44,64]

4.3. AMPs in CRS

CRS is a complex inflammatory condition of the paranasal sinuses that persists for 12 weeks or longer, often leading

to significant morbidity and reduced quality of life. The pathogenesis of CRS involves a dysregulated immune response, microbial colonization, and impaired mucosal defense mechanisms. Among the key players in the innate immune defense of the sinonasal mucosa are AMPs, which are small, cationic molecules that play a critical role in combating pathogens and modulating inflammation. AMPs are produced by epithelial cells and immune cells, and their expression is often altered in CRS, contributing to the disease's persistence and severity.[65-68]

4.4. Defenses in CRS

The sinonasal epithelium serves as the first line of defense against inhaled pathogens, allergens, and environmental irritants. In CRS, this barrier function is often compromised, leading to increased susceptibility to infections and chronic inflammation. AMPs are a crucial component of this defense system, providing rapid, non-specific immunity against bacteria, viruses, and fungi.[65]

4.5. Cathelicidins in CRS

In CRS, the expression of LL-37 is often altered, with studies showing both increased and decreased levels depending on the subtype of CRS (e.g., with or without nasal polyps). In CRS with nasal polyps, LL-37 levels are typically reduced, which may contribute to the impaired antimicrobial defense and increased bacterial colonization observed in these patients. Conversely, in CRS without nasal polyps, LL-37 expression may be upregulated as part of the inflammatory response. The dysregulation of cathelicidins in CRS highlights their potential role in the disease's pathogenesis and their potential as therapeutic targets.[69,70]

4.6. Deleted in malignant brain tumors 1 (DMBT-1) in CRS

In CRS, the expression of DMBT-1 is often downregulated, particularly in patients with nasal polyps. This reduction in DMBT-1 levels may impair the sinonasal epithelium's ability to clear pathogens and maintain mucosal homeostasis, contributing to the chronic inflammation and microbial colonization seen in CRS. In addition, DMBT-1 has been shown to interact with other AMPs and immune mediators, suggesting that its dysregulation may have broader implications for the immune response in CRS.[71,72]

4.7. S-100 proteins in CRS

In CRS, specific S-100 proteins, such as S100A7 (psoriasin) and S100A8/A9 (calprotectin), have been implicated in the disease's pathogenesis. S100A7 is an AMP that exhibits antimicrobial activity against bacteria and fungi, and its expression is often increased in CRS, particularly in patients with nasal polyps. The role of S-100 proteins in CRS underscores the complexity of the immune response in this condition and highlights their potential as biomarkers or therapeutic targets.[65]

4.8. Indolicidin in CRS

Indolicidin exhibits immunomodulatory properties by influencing cytokine production and promoting wound healing, which could aid in the repair of damaged sinus mucosa. However, its role in CRS remains under investigation, with studies exploring its potential as a therapeutic agent to combat persistent infections and inflammation.

4.9. CP10A in CRS

CP10A, a synthetic analog of the cathelicidin family of AMPs, has demonstrated significant antimicrobial and anti-inflammatory effects. In CRS, CP10A has been shown to inhibit biofilm formation, a key factor in the persistence of chronic infections. Its ability to modulate the immune response by reducing pro-inflammatory cytokines such as IL-6 and TNF-α makes it a promising candidate for managing CRS-related inflammation. Furthermore, CP10A's stability and low toxicity profile enhance its potential for clinical application in sinusitis treatment.[69]

4.10. Tachyplesin in CRS

In CRS, tachyplesin's ability to neutralize lipopolysaccharides and inhibit biofilm formation may help alleviate chronic infections. Its immunomodulatory effects, including the suppression of excessive inflammatory responses, further highlight its potential as a therapeutic agent in CRS management.

4.11. Microcins in CRS

In CRS, microcins may play a role in modulating the sinus microbiome by targeting pathogenic bacteria while sparing commensal species. This selective antimicrobial activity could help restore microbial balance in the sinuses, thereby reducing chronic inflammation. Research into the application of microcins in CRS is still in its early stages, but their potential for targeted therapy is promising.[73]

4.12. PR-39 in CRS

In CRS, PR-39 has been shown to promote tissue repair and reduce inflammation by modulating the activity of immune cells and inhibiting the production of reactive oxygen species. Its ability to enhance epithelial regeneration and restore mucosal integrity makes it a potential therapeutic candidate for managing the chronic inflammatory and tissue-damaging processes associated with CRS.[74,75]

4.13. Sinus mucus secretion composition to combat CRS

CRS is a complex inflammatory condition of the paranasal sinuses characterized by persistent symptoms and mucosal dysfunction. The sinus mucus, a critical component of the innate immune system, plays a pivotal role in defending against pathogens and maintaining sinus health. Understanding the specific components of sinus mucus and their roles in CRS pathogenesis is essential for developing targeted therapeutic strategies.[75-77] The composition of sinus mucus and its immune components plays a critical role in the pathogenesis of CRS. Understanding the roles of lysozyme, lactoferrin, secretory leukocyte proteinase inhibitor (SLPI), TLRs, NLRs, and other immune molecules provides valuable insights into the mechanisms underlying CRS and offers opportunities for developing targeted therapies to restore mucosal defense and reduce inflammation.

4.14. Lysozyme in CRS

In CRS, lysozyme levels are often dysregulated, with studies showing both increased and decreased expression depending on the disease phenotype. Reduced lysozyme activity may compromise the mucus barrier, allowing bacterial colonization and biofilm formation, which are common in CRS. Conversely, elevated lysozyme levels may contribute to tissue damage due to excessive inflammation. Restoring lysozyme homeostasis is a potential therapeutic target to enhance mucosal defense in CRS.[78]

4.15. Lactoferrin in CRS

In CRS, lactoferrin expression is often altered, with some studies reporting reduced levels in patients with severe disease. Lactoferrin's ability to modulate immune responses and protect against microbial invasion makes it a promising candidate for therapeutic interventions in CRS.[79]

4.16. SLPI in CRS

In CRS, SLPI levels are often diminished, particularly in patients with neutrophilic inflammation or recurrent infections. The loss of SLPI activity may exacerbate tissue damage and impair mucosal repair, highlighting its importance in maintaining sinus health. Augmenting SLPI levels could help mitigate inflammation and promote healing in CRS.[80,81]

4.17. Other immune system components to combat CRS

In addition to lysozyme, lactoferrin, and SLPI, sinus mucus contains other immune components such as defensins, cathelicidins, and immunoglobulins that contribute to mucosal defense. Defensins and cathelicidins are AMPs that directly kill pathogens and modulate immune responses. Immunoglobulins, particularly immunoglobulin A, play a crucial role in neutralizing pathogens and preventing their adherence to mucosal surfaces. Dysregulation of these components in CRS can impair the mucus barrier and exacerbate disease severity. Targeting these immune molecules may offer novel therapeutic avenues for CRS management.[4,82] In CRS, TLR expression and signaling are often dysregulated, contributing to aberrant immune activation and chronic inflammation. For example, TLR2 and TLR4 are implicated in recognizing bacterial components such as lipopeptides and lipopolysaccharides, respectively.[83] NLRs are intracellular sensors that detect microbial components and cellular damage, triggering inflammatory responses through the formation of inflammasomes. In CRS, NACHT, LRR, and PYD domains-containing protein 3 (NLRP3), inflammasome activation has been linked to the release of pro-inflammatory cytokines such as IL-1β and IL-18, which drive chronic inflammation.[76]

4.18. Future directions: Elucidating the pathogenesis of antimicrobial dysregulation in CRS

While the downregulation of key AMPs and lipids in the sinonasal epithelium of CRS patients is well-documented, the precise upstream mechanisms driving this critical immune defect remain inadequately defined. To further elucidate the pathogenesis of CRS, future research must delve beyond correlation and uncover the exact causal mechanisms responsible for this dysregulated expression. A primary area of investigation should focus on identifying modifications in the intracellular signaling pathways that govern AMP and lipid synthesis. For example, it is crucial to determine whether defects exist in the TLR, IL-related (e.g., IL-4/IL-13 through signal transducer and transcription activator 6), or epidermal growth factor receptor pathways, which directly modulate the transcription of molecules such as β-defensins and S100 proteins. Furthermore, the role of disruptions in intercellular communication warrants exploration; this includes examining how altered crosstalk between epithelial cells, immune cells (e.g., T-cells and macrophages), and the microbiome through cytokine networks or gap junctions can perpetuate a state of immune tolerance or suppression. In addition, the impact of elevations in metabolic stress within the inflammatory sinus environment should be considered. Hypoxia, nutrient deprivation, and oxidative stress can activate pathways such as hypoxia-inducible factor 1-alpha and 5'-AMP-activated protein kinase, which may inadvertently suppress energy-intensive host defense mechanisms. Systematic investigation into these areas—

through targeted in vitro models, animal studies, and analysis of human tissue samples—will not only provide a more coherent understanding of CRS pathogenesis but also reveal novel, druggable targets to restore the innate immune barrier and break the cycle of inflammation and microbial colonization that characterizes this debilitating disease.

4.19. Lifestyle in CRS susceptibility

While the primary triggers for cytokine release syndrome are often linked to specific immunotherapies (e.g., chimeric antigen receptor T-cell [CAR-T cell] therapy and bispecific antibodies) and underlying tumor burden, a comprehensive understanding of its incidence requires looking beyond these immediate factors. Subtle determinants such as host genetics, environmental exposures, and lifestyle factors may also influence the inflammatory milieu and immune reactivity in cytokine release syndrome. The interplay of host genetic predispositions, environmental exposures, and lifestyle choices can significantly modulate an individual's susceptibility to CRS, its severity, and clinical trajectory. Integrating these elements into the discussion provides a more holistic and personalized framework for risk stratification and management.

4.20. Host genetic predispositions

Individual genetic variation plays a fundamental role in determining the intensity of immune responses. Polymorphisms in genes encoding cytokines, their receptors, and key signaling molecules can create a pro-inflammatory "set-point" that predisposes patients to severe CRS. For example, single-nucleotide polymorphisms in the promoters of *IL-6* and *TNFA* can lead to heightened expression on immune activation. Similarly, variations in genes involved in TLR signaling or the NLRP3 inflammasome pathway may lower the threshold for uncontrolled macrophage and monocyte activation, a key driver of CRS. Future research, and indeed the discussion of CRS incidence, would be strengthened by considering how such germline genetics interact with therapeutic triggers to determine clinical outcomes.

4.21. Environmental influences and the microbiome

The patient's environment, particularly the composition of their gut microbiome, is emerging as a critical modulator of systemic immunity. A diverse, commensal-rich microbiome helps maintain immune homeostasis and regulates inflammatory pathways. In contrast, dysbiosis—often induced by prior broad-spectrum antibiotic use, dietary patterns, or other environmental factors—can skew the immune system toward a hyperinflammatory state. This "primed" immune background may exacerbate the cytokine storm following CAR-T-cell infusion or bispecific antibody engagement. Investigating and discussing the impact of microbiome status, along with other environmental exposures such as prior viral infections (e.g., cytomegalovirus and Epstein–Barr virus) that shape the T-cell repertoire, could provide valuable insights into inter-patient variability in CRS incidence.

4.22. The role of lifestyle and comorbidities

Lifestyle factors and pre-existing comorbidities represent another layer of complexity. Chronic conditions such as obesity, metabolic syndrome, and cardiovascular disease are associated with a state of low-grade, systemic inflammation, characterized by elevated baseline levels of C-reactive protein, IL-6, and other acute-phase reactants. This pre-activated inflammatory state may serve as a catalyst, amplifying the cytokine cascade initiated by immunotherapy. Furthermore, lifestyle choices such as smoking, chronic alcohol consumption, and nutritional status (e.g., Vitamin D deficiency) can impair immune regulation and endothelial integrity, potentially worsening CRS severity and contributing to related complications such as capillary leak syndrome.

4.23. Host genetic factors

Emerging evidence underscores the significant contribution of heritable factors to CRS susceptibility. Polymorphisms in genes governing the innate and adaptive immune response can profoundly alter an individual's reaction to sinonasal insults. For example, variations in genes encoding TLRs, which are crucial for pathogen recognition, may lead to a blunted or exaggerated inflammatory response to common allergens and microbes. Similarly, alterations in the cystic fibrosis transmembrane conductance regulator gene, even in subclinical, non-cystic fibrosis forms, can impair mucociliary clearance, creating a permissive environment for persistent inflammation. Furthermore, genes involved in epithelial barrier function, such as those encoding filaggrin, and in the regulation of Th cell differentiation (e.g., toward a Th2-dominant phenotype in CRS with nasal polyps) are areas of active investigation. A more comprehensive genetic characterization of patient cohorts could enable risk stratification and identify novel therapeutic targets for specific endotypes of CRS.

4.24. Environmental influences

The external environment serves as a constant source of challenge to the sinonasal epithelium. Chronic exposure to airborne pollutants, including particulate matter (PM2.5 and PM10), nitrogen dioxide, and ozone, has been correlated with an increased prevalence and severity of CRS. These pollutants are thought to induce oxidative

stress, directly damage the ciliated respiratory epithelium, and act as adjuvants that potentiate allergic inflammation. Occupational exposures represent another critical dimension; individuals in professions involving dust (e.g., wood and flour), chemical fumes, and other irritants are demonstrably at higher risks. Moreover, the role of the indoor microbiome and early-life exposure to a diverse microbial environment (the "hygiene hypothesis") may be pivotal in shaping immune tolerance, with implications for the development of atopic conditions, including CRS.

4.25. Lifestyle and comorbid behaviors

Lifestyle choices and associated comorbidities are modifiable factors that can significantly impact CRS incidence and disease course. Smoking, both active and passive, is a well-established risk factor, as it paralyzes cilia, increases mucus viscosity, and promotes neutrophilic inflammation. Dietary patterns may also play a role; diets high in refined sugars and saturated fats may promote a pro-inflammatory state, while diets rich in antioxidants and omega-3 fatty acids could have a protective effect. The management of comorbid conditions is equally critical. Poorly controlled gastroesophageal reflux disease may contribute to CRS through the direct irritation of the posterior pharynx and sinonasal mucosa with refluxate. Furthermore, psychological stress, which can dysregulate immune function, and inadequate sleep are increasingly recognized as factors that may exacerbate symptom burden and hinder treatment response.

5. Conclusion

Microbial interactions are central to the pathogenesis of CRS, influencing disease onset, progression, and persistence. CRS can be reframed as a disease of failed host–microbe communication, driven by dysregulated immune responses with cancer-like features. This review highlights the role of microbial interactions in the pathogenesis of CRS, focusing on the interaction between the host immune system and microbial communities. We emphasize the importance of AMPs and antimicrobial lipids in maintaining sinus homeostasis and their potential disruption in CRS. This review synthesizes current knowledge on how microbial interactions influence immune responses, including the modulation of AMPs and lipids, and their contribution to chronic inflammation. We also highlight emerging therapeutic strategies targeting microbial–immune interactions to restore sinus health. By integrating findings from recent studies, this article provides a comprehensive overview of the molecular mechanisms underlying CRS and highlights the importance of microbial–immune interactions in disease progression and management.

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