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The Specific Role of Immunological Processes in the Development of Chronic Purulent Rhinosinusitis

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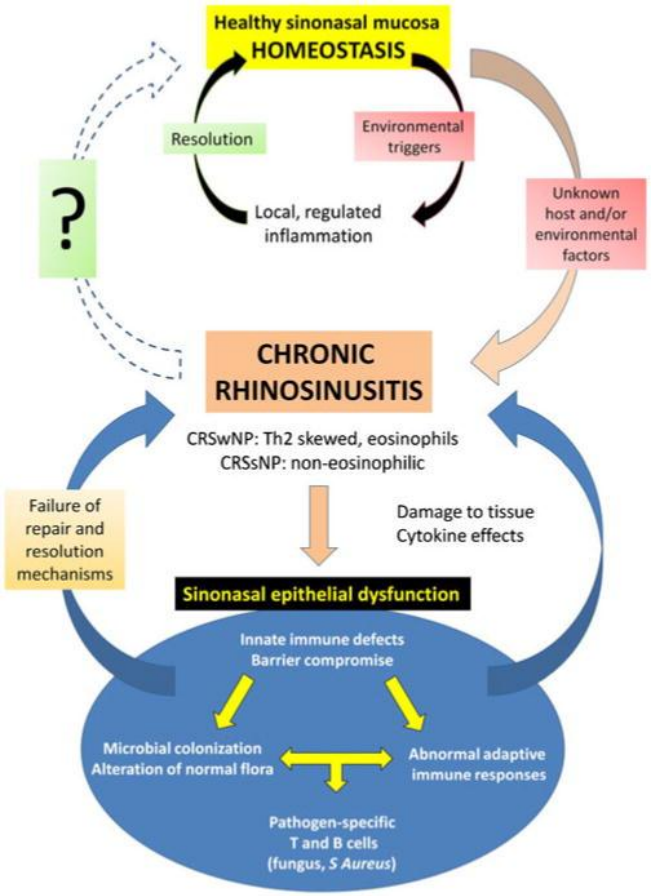
Abstract: Chronic rhinosinusitis (CRS) is a prevalent health condition characterized by sinonasal mucosal inflammation lasting at least 12 weeks. Heterogeneous in clinical presentation, histopathology, and therapeutic response, CRS represents a spectrum of disease entities with variable pathophysiology. Increased knowledge of cellular and molecular derangements in CRS suggests potential etiologies and targets for therapy. Microbial elements including fungi, staphylococcal enterotoxin, and biofilms have been implicated as inflammatory stimuli, along with airborne irritants and allergens. Defects in innate immunity have gained increased attention as contributors to the chronic inflammatory state. A combination of host susceptibility and environmental exposure is widely believed to underlie CRS, although direct evidence is lacking. Presently, without precise disease definitions and identifiable universal triggers, CRS pathogenesis is broadly described as multifactorial. Current research is beginning to unravel complex and diverse effects of chronic inflammation on sinonasal mucosal homeostasis, but dysfunctional pathways of inflammatory regulation and resolution require further elucidation.

Keywords: Chronic rhinosinusitis, Inflammation, Innate immunity, Host defense, Epithelium.

Introduction

Despite its prevalence and significant health impact, the etiology of chronic rhinosinusitis (CRS) remains incompletely understood. Unlike acute bacterial sinusitis, for which the pathophysiology is well-defined, CRS is a heterogeneous condition characterized broadly by persistent inflammation of the sinonasal mucosa [1]. It is widely believed that the causes of inflammation in CRS are diverse and multifactorial, relating to overlapping host and environmental triggers. Disruption of normal epithelial function subsequent to inflammation of any origin can result in mucostasis and microbial colonization. Infection, in turn, stimulates further inflammation and exacerbates the chronic disease process. Current research in the field has attempted to elucidate the factors driving persistent sinonasal inflammation [2], highlighting the complex interplay between the environment and innate and adaptive mucosal immune mechanisms [3]. It is increasingly recognized that CRS is not a single disease entity, but instead varies widely in clinical presentation, histopathology, and response to therapy. Multiple pathophysiologic pathways likely exist that can result in the common endpoint of sinonasal mucosal inflammation (Fig. 1). Perhaps more importantly, once chronic inflammation becomes manifest, secondary activation of additional pathophysiologic pathways inevitably blurs identification of the initiating cause. The determination of which cellular and molecular features of CRS represent underlying factors inducing inflammation or merely downstream consequences remains an ongoing challenge in the growing field of CRS research. The goal of this review is to present the variety of exogenous and endogenous factors that have been implicated in CRS pathogenesis and discuss them in light of the recent literature.



CRS: Definition, Epidemiology, and Cellular Characteristics

Rhinosinusitis is among the most common conditions in the United States, affecting more than 31 million people annually [4]. Chronic rhinosinusitis prevalence, however, is difficult to extrapolate because of the heterogeneity of its presentation and imprecise diagnosis. Conservative estimates indicate that CRS is responsible for 18 to 22 million office visits annually, presenting a considerable economic and health care burden [5]. CRS is defined as an inflammatory process of the nose and paranasal sinus mucosa for at least 12 consecutive weeks. The diagnosis of CRS is clinical, based on subjective and objective findings, such as those recommended in guidelines published by the American Academy of Otolaryngology— Head and Neck Surgery [1]. Although these criteria are helpful in setting a framework for diagnosis and therapy, the correlation between symptoms and the degree of inflammation in CRS is not strong.

Inflammation Induced by Microbial and Environmental Factors

The sinonasal epithelium is in constant contact with the outside environment and serves as the first line of defense against inhaled pathogens and particulates. This interaction involves a complex set of innate and adaptive immune pathways at the mucosal surface driving inflammatory responses that protect the host from infection [13]. Although these mechanisms are essential to maintain homeostasis, inappropriate activation or lack of inhibition can lead to chronic inflammation that may be counterproductive and causative of symptoms. Because microbial elements are frequently observed in association with CRS, it is widely speculated that infection plays a role as an initiator of inflammation, or at least contributes to its persistence. At the same time, because the nose normally functions as a filter, the transient presence of incidental microorganisms and particulates is not necessarily pathologic. It remains unanswered whether pre-existing inflammation with impairment of mucociliary clearance is responsible for retention of microbial and environmental materials in CRS, or whether these agents in fact stimulate inflammation.

Inflammation Caused by Intrinsic Host Factors

The vast majority of CRS is idiopathic in origin, with only a minority of cases caused by identifiable genetic disorders (eg, cystic fibrosis, ciliary dyskinesia) or systemic inflammatory processes (eg,

sarcoidosis, Wegener's granulomatosis) [15,]. Ultimately, regardless of the cause, the defining characteristic of CRS is inflammation of the sinonasal mucosa with obstruction of sinus outflow. Current medical and surgical therapies that target inflammation and infection are effective for the majority of CRS patients, but for those in whom all treatments are ineffective or the response is not durable, various mechanisms have been invoked to explain persistent inflammation. The high incidence of radiographic and pathologic evidence of osteitis in CRS (53%) has been cited as supporting evidence that bony inflammation plays a role [16]. Increasingly, CRS may develop in the context of previous surgery, where mucosal trauma and bony exposure can be the impetus for poor healing and ongoing mucosal dysfunction. CRSwNP patients undergoing revision surgery have a significantly higher incidence of osteitis than in patients undergoing primary surgery [15], which may either imply a relationship between osteitis and disease severity, or alternatively may reflect the fact that surgery itself increases the incidence of osteitis.

In the final analysis, inflammation in CRS appears to arise from abnormalities of normal mucosal immune function that disrupt maintenance of homeostasis. Although several interesting observations have been made that shed light on potential inflammatory mechanisms and suggest different host-centered hypotheses of CRS pathogenesis, it must again be recognized that characterization of the active disease state does not necessarily imply causality. Just as with putative infectious triggers, many host derangements identified in a chronic state of sinonasal mucosal disequilibrium may reflect downstream effects of inflammation, rather than the basis of the disease.

Adaptive Immunity

Chronic sinonasal inflammation is associated with lymphocytic infiltration and prominent expression of inflammatory cytokines [1]. Although it is recognized that CRSwNP and CRSsNP have distinct mediator profiles and cellular phenotypes, the mechanism underlying polarization into T-helper cell subtype responses is unknown. Naïve T cells differentiate into memory and effector cells upon interaction with antigen presenting cells in the context of specific co-stimulatory signals provided by cytokines and ligand-receptor interactions. Th1 cells characteristically secrete interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), which potently activate macrophages and cytotoxic T cells, and promote B-cell antibody production. Th2 cells secrete IL-4, IL-5, IL-9, and IL-13, which promote eosinophil survival and activation, as well as production of IgE. Investigation of cytokine expression in CRS has revealed both Th1 and Th2 cytokines, reflecting crosstalk between the two inflammatory responses. In addition to T and B cells, dendritic cells are important components of the adaptive immune system within the sinonasal mucosa. Sinonasal mucosal dendritic cells likely play a critical role in local T- and B-cell differentiation. B-cell proliferation and antigen-specific IgE are increased in polyps, and up-regulation of B-cell activators and proliferation factors are described in patients with CRSwNP in comparison to those with CRSsNP and controls [12]. Increased proliferation and maturation of B cells promotes immunoglobulin isotype switch recombination, potentially exacerbating eosinophilic inflammation in CRSwNP. A relative deficit of myeloid dendritic cell subsets in CRSwNP has been thought to favor priming of T cells to a Th2 phenotype contributing to persistent inflammation [13•]. The epithelium communicates with dendritic cells via thymic stromal lymphopoetin and other inflammatory cytokines and signaling molecules.

Sinonasal Epithelial Cell Innate Immune Function

Deficiencies in the antimicrobial activity of the sinonasal mucosa can create a permissive environment for microbial colonization. Pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) allow sinonasal epithelial cells (SNEC) to detect and initiate responses against pathogens present in the airway lumen. Messenger RNA (mRNA) for all 10 TLRs have been identified in SNECs, and their function has been demonstrated by induced production of innate immune effectors such as human β-defensin 2, serum amyloid A, and surfactant proteins A and D [14]. The activity of SNEC TLRs is abnormally diminished in recalcitrant CRSwNP [15–17]. In addition, expression of the antimicrobial protein, lactoferrin, is decreased at the mRNA and protein level in the nasal mucosa of CRS patients [18•,]. Although decreased antimicrobials may contribute to colonization, abnormal innate immune responses of SNEC may also promote inflammation through stimulation of adaptive immune elements and effector leukocytes.

Conclusions

CRS is a commonly diagnosed health condition with a significant impact on quality of life, but the highly heterogenous nature of the disease confounds identification of an underlying cause. Numerous potential etiologic and disease-modifying factors have been proposed in CRS, leading to a belief that the chronic inflammation must be multifactorial. Certainly, a complex interplay normally exists between the host and the environment at the boundary surfaces of the sinonasal tract, and homeostasis requires a properly functioning mucosal immune system. Episodic inflammatory responses must be precisely regulated and terminated to control infectious threats without damaging the host. In CRS, when inflammation is perpetually unresolved, homeostatic balance cannot be restored, resulting in a state of immune disequilibrium. Study of chronically inflamed CRS tissue reveals numerous cellular and molecular derangements of host defense and repair mechanisms, which in turn are associated with alterations in microbial flora. Abnormalities in the adaptive immune response likely contribute importantly to the chronicity of the disease process. At the current time, the initial drivers of inflammation in CRS remain unclear, but the local features of the chronically inflamed epithelium are becoming better characterized. Although CRS is currently perceived as multifactorial in origin, a more complete understanding of the pathophysiology of active CRS will allow differentiation among disease initiators, disease modifiers, and unrelated epiphenomena. Ultimately, identification of the etiologic factors responsible for initiating inflammation in CRS may be less important than elucidation of deficient pathways responsible for its down-regulation and resolution.

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