

A superantigen hypothesis for the pathogenesis of chronic hypertrophic rhinosinusitis, allergic fungal sinusitis, and related disorders

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Background: Chronic eosinophilic-lymphocytic respiratory mucosal inflammatory disorders include hypertrophic sinus disease, allergic fungal sinusitis, allergic bronchopulmonary aspergillosis, and chronic severe asthma. They have many analogous or shared aspects of pathology at molecular, cellular, and clinical levels of analysis.

Objective: To propose a theory, and supporting data through comprehensive literature review, that unifies these diseases' pathogenesis.

Methods and Data Sources: Current medical literature was used as supportive background information. Reinterpretation of existing studies and reasoned speculation were used when necessary and identified where used. English language MEDLINE articles that referenced sinusitis, rhinosinusitis, allergic fungal sinusitis, asthma, allergic bronchopulmonary aspergillosis, nasal polyp, superantigen, and T cell receptor from 1983 to present were potentially used as background or supportive information. Additional referenced articles, published abstracts, and National Center for Biotechnology Information Entrez protein database searches were used. Case reports, studies, review articles, and textbooks were included.

Results: Multiple lines of evidence support the proposed hypothesis that microbial T cell superantigen production, persistence, and host-responsiveness are the fundamental components that unify the pathogenesis of all common chronic eosinophilic-lymphocytic respiratory mucosal inflammatory disorders. Superantigen amplification of preexisting immunopathology is the proposed mechanism for disease induction and maintenance. Preexisting immunopathology is created in the individual by a potential heterogeneity of immunopathologic signals that can include type I immediate hypersensitivity, other antigen-specific immune responses, cytokine dysregulation, eicosanoid dysregulation, various genetic mutations, and other molecular pathology. Although the ability to develop chronic severe inflammatory disease is dependent upon this immunopathology, host T cell receptor V β genetics and persistent superantigen production/exposure at the respiratory mucosa by relevant superantigen-producing extra- or intracellular microbes are postulated to be required. This mechanism for disease pathogenesis may also apply to other disorders. Approaches to prove this theory and its predictions are presented.

Conclusions: The pathogenesis of all the disorders discussed can be unified through the superantigen hypothesis proposed. Multiple lines of evidence support this hypothesis. How we view these common conditions will change, and new research into pathogenesis and treatment will occur if this proves true.

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INTRODUCTION

Chronic rhinosinusitis has an incidence of approximately 15% in the United

States, affecting >30 million Americans.¹ There are approximately 200,000 surgeries for chronic rhinosinusitis per

year. Direct yearly health care costs are approximately \$2.4 billion excluding the costs of surgery.¹ Despite 13 million antibiotic prescriptions written per year for the medical treatment of chronic rhinosinusitis, many patients remain clinically refractory and surgically recurrent. Yet, it is unclear what roles microorganisms really play in many of these patients. Although many immunocompetent patients with chronic rhinosinusitis have an underlying anatomical etiology for their disease, such as osteomeatal unit obstruction or nasal septal deviation, a significant proportion of these patients continue to have chronic rhinosinusitis despite surgical and antibiotic treatments. These patients have "hypertrophic" or "hyperplastic" sinus disease (HSD) and exhibit recurring cycles of sinonasal mucosal hypertrophy and hyperplasia. Other terms for this condition have included "noninfectious sinusitis" and "chronic hyperplastic sinusitis/nasal polyposis." Patients with HSD clinically present with chronic rhinosinusitis and nasal polyps. Often, they are atopic,^{2,3} have asthma,⁴ and have a history of multiple sinus surgeries.

The sinus mucosa in HSD contains a chronic inflammatory infiltrate consisting of small lymphocytes, plasma cells, and eosinophils,⁵ similar to that seen in asthmatic bronchial mucosa (Fig 1). This is not the type of inflammatory reaction typically associated with true tissue-invasive bacterial infection that would include neutrophilic infiltrates, microabscess formation, and tissue necrosis.^{6,7} The inflammation present in HSD can therefore be histopathologically termed "allergic inflammation" or "asthmatic inflam-

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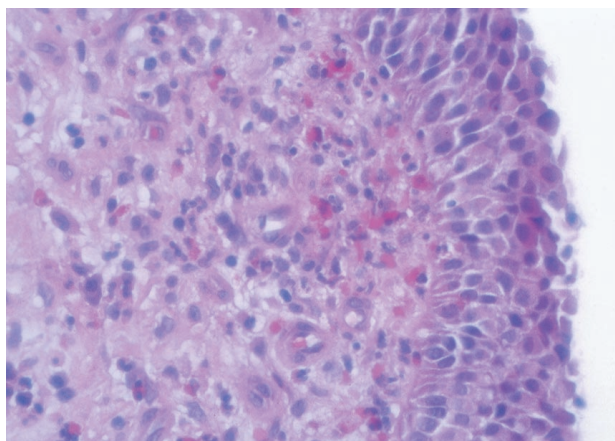


Figure 1. Sinus mucosa from a representative patient with HSD. The characteristic inflammatory infiltrate of lymphocytes and eosinophils (cells with red cytoplasm) is seen. This patient was nonatopic. Hematoxylin and eosin stain, $\times 400$.

mation.” It has been postulated that HSD represents a disorder of TH2 activation, similar to that of asthma.^{5,8} In situ sinus mucosal lymphocyte cytokine analysis from allergic and nonallergic patients with HSD has shown a pattern of TH1 and TH2 activation similar to that found in bronchoalveolar lavage (BAL) lymphocytes from allergic and nonallergic asthmatic patients, with allergic patients showing TH2 predominance and nonallergic patients showing TH1 predominance.^{9,10} Patients with HSD also often have asthma, often develop wheezing as the sinusitis worsens, and develop increased total serum immunoglobulin (Ig)E levels and peripheral eosinophil counts proportional to the severity of the sinusitis as measured by radiographic parameters.^{8,11} Further evidence for the association of HSD with asthma comes from the clinical syndrome called aspirin triad.^{12,13} This syndrome presents a pathophysiologic link between asthma, HSD, and aspirin hypersensitivity. Aspirin hypersensitivity is thought to involve dysregulation of leukotriene biosynthesis and/or responsiveness.^{14,15} Although the histopathologic features of all patients with HSD are those of allergic inflammation, the role of type I immediate hypersensitivity has been questioned.^{16,17}

Another line of evidence linking the pathophysiology of HSD to asthma

comes from recent work on allergic fungal sinusitis (AFS). AFS is a chronic HSD that has an estimated incidence of 5 to 10% of all chronic sinusitis going to surgery, particularly in endemic areas such as the southern or southwestern United States.^{18–20} It is characterized as a chronic allergic inflammatory reaction to the presence of a fungus (usually dematiaceous fungi) found in allergic mucin within the sinus cavities. The sinus mucosal infiltrate of small lymphocytes, plasma cells, and eosinophils in AFS is identical to other patients with HSD, and to the bronchial mucosa in asthma.²⁰ The immunopathophysiology of AFS has been shown to be analogous to allergic bronchopulmonary aspergillosis (ABPA).^{20,21} ABPA is a disorder characterized by an immunologic and allergic asthmatic response to the presence of the mold *Aspergillus fumigatus* growing within bronchial allergic mucin. ABPA is seen in conjunction with asthma and often produces oral corticosteroid dependency. Analogously, patients with AFS have HSD which is often refractory and surgically recurrent, and most have asthma.²⁰ Both AFS and ABPA patients have elevated polyclonal total serum IgE and fungal-specific IgG levels along with other related immunopathologic findings.²⁰ Further, the treatment for AFS has been modeled after the treatment for

ABPA, using oral corticosteroids rather than antifungal drugs.^{22,23}

Despite decades of work, the pathogenesis of many forms of asthma remains unknown. The role of type I immediate hypersensitivity, TH1/TH2 cytokine dysregulation, leukotriene dysregulation, infectious disease, and genetics are some of the current areas of research focus. Similar research into HSD has only recently begun.

Microbes in HSD and AFS

Bacterial infection is clearly implicated in acute sinusitis, but its role has been questioned in the etiology of HSD.^{5,24,25} Although bacterial infection is felt to be doubtful as a primary etiology for HSD, aerobic maxillary cultures grow *Staphylococcus aureus* most often, followed by α -hemolytic streptococci, *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, and *Haemophilus spp.*²⁶ Most HSD cultures are also positive for anaerobes including *Peptostreptococcus spp.*, *Prevotella spp.*, *Fusobacterium spp.*, and *Propionibacterium acnes*.

AFS patients commonly culture *S. aureus* from surgical sinus cultures in addition to the AFS organism.²⁰ However, *S. aureus* sinus mucosal infection has not been felt to be of clinical importance in AFS because the disorder was reported refractory to antistaphylococcal antibiotics and the clinical presentation, surgical sinus histopathology and immunologic findings were not consistent with bacterial infection.²⁰ Eosinophilic-lymphocytic mucosal inflammation, the presence of type I immediate hypersensitivity, elevated total serum IgE, and fungal-specific IgG were characteristic.²⁰ Yet, *Bipolaris spicifera* fungal-specific IgE levels in *B. spicifera* AFS were no higher than in patients with type I immediate hypersensitivity to *B. spicifera* but without AFS.²⁰ This questions the role of fungal-specific IgE as the only factor in the generation of the extensive and recurring allergic sinus mucosal inflammation with associated sinus mucosal hypertrophy and hyperplasia that typifies AFS.

If microbes are present in surgical sinus cultures from many patients with HSD, especially the etiologic fungi in AFS, and mucosal-invasive infection with these microbes is not apparent, then what is the role for these microbes? Either they are passive and not etiologic at all, or they participate in the pathogenesis of HSD through other mechanisms. This has clearly been shown with fungi present histopathologically within the sinus cavities in AFS, in which associated sinus mucosal allergic inflammation, extramucosal allergic mucin, and absence of tissue invasion are all required for diagnosis.²⁰

Superantigens

T cell superantigens are microbial toxins that bind to human leukocyte antigen (HLA) class II histocompatibility molecules on antigen-presenting cells (APC) and T cell receptors (TCR) on T cells simultaneously, bypassing classical antigen specificity and causing APC-induced activation of T cells²⁷⁻²⁹ (Fig 2). However, superantigens can also serve as classical antigens because antisuperantigen antibodies are often concomitantly elicited. The HLA class II molecule binding area for superantigens is on the outside of the α chain, away from the peptide antigen-specific binding region. The TCR binding area for superantigens is also usually away from the antigen-specific area of the molecule, on the outside of the β chain variable ("TCR V β ") region, although *Mycoplasma* superantigen does bind to the antigen-specific region of the TCR V β chain.³⁰ The superantigen-binding area on the TCR V β chain is coded in the germ line, with different individuals carrying specific alleles of TCR V β genes that differ depending on inheritance. Common TCR V β genes that can bind microbial superantigens in the human include TCR V β 2, 3, 5.1, 6.7, 8, 12, 13.1, 13.2, and 17.^{29,31} Many superantigens are capable of binding to a number of different TCR V β gene motifs which can lead to activation of up to 30% of all T cells in a given individual. This contrasts with antigen-specific T cell responses which occur at a frequency of <0.01%.³² Subse-

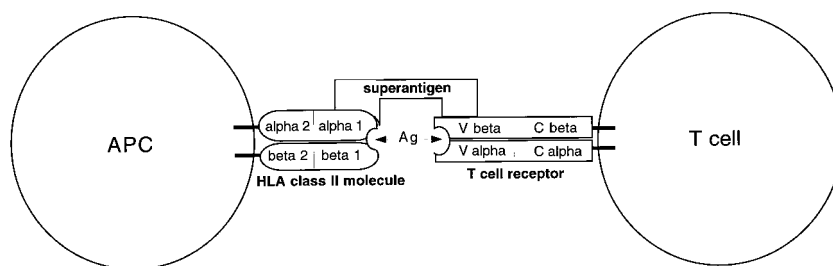


Figure 2. T cell superantigen mechanism of action. APC, antigen-presenting cells; Ag, peptide antigen-specific binding areas. Both the HLA class II molecule and TCR are heterodimers with constant and variable regions. Microbial superantigens bind to the sides of the HLA class II molecule α 1 chain and TCR V β chain simultaneously, bypassing antigen specificity and leading to T cell activation.³³

quent extensive superantigen-dependent T cell activation can cause systemic toxicity and is a mechanism of microbe-induced disease. Some TCR V β motifs are capable of being bound by a variety of different microbial superantigens.^{29,31} Common microbial superantigens include *S. aureus* enterotoxins which cause food poisoning eg, staphylococcal enterotoxin B (SEB) and toxic shock syndrome (TSST-1). Both rabies virus and Epstein-Barr virus have superantigenic activity, and endogenous viral superantigens are common in mice.³³ Many superantigens remain undiscovered, however, as evidenced by the recent finding of human retroviral superantigens in human breast cancer,³⁴ type I diabetes,³⁵ and multiple sclerosis,³⁶ the recent discovery of *S. aureus* enterotoxin J,³⁷ and the very recent report of many additional superantigens found by *S. aureus* whole-genome sequencing.³⁸

Atopic dermatitis is a chronic inflammatory dermatitis found primarily in atopic individuals that cultures positive for enterotoxin superantigen-producing strains of *S. aureus* in a majority of patients, who also produce anti-enterotoxin IgE.^{39,40} An elevated polyclonal total serum IgE level is the most common laboratory abnormality found. T cells from all patients tested were found to carry the proper TCR V β motifs for *S. aureus* superantigen-binding and to produce interleukin (IL)-5 upon stimulation with monoclonal antibodies specific for the corresponding TCR V β motifs.⁴¹ Current evidence suggests that these superantigens

play a role in the pathogenesis of atopic dermatitis in many, if not most, patients.³⁹⁻⁴¹ Microbial superantigens have previously been implicated in the pathogenesis of Kawasaki disease,^{42,43} psoriasis,⁴⁴⁻⁴⁶ and rheumatoid arthritis.^{47,48}

Evidence Consistent with Immune Activation by T Cell Superantigens

It has recently been shown that patients with severe asthma have BAL T cells that show a restricted heterogeneity of TCR V β motifs.⁴⁹ The TCR V β motifs found were those capable of binding to common microbial superantigens. T cells bearing these TCR V β motifs were not preferentially present in BAL from patients with milder asthma. Although strongly suggestive of superantigen-induced recruitment of correspondingly responsive T cells into the lung in patients with severe asthma, this study was not designed to test for the presence of either microbes or superantigens. The local persistence of specific intracellular microbes has already been implicated in severe asthma, including *Mycoplasma*, adenovirus, and *Chlamydia pneumoniae*.⁵⁰

Recent work in Balb/C mice has confirmed that bronchial airways hyperresponsiveness and the typical histopathologic findings of asthma could be induced by the aspiration of the well known superantigen SEB.⁵¹ This is the first study to show that eosinophilic-lymphocytic asthmatic respiratory mucosal inflammation together with measurable airways hyperresponsiveness can be induced by a microbial superantigen. It is also known that SEB stim-

ulates the release of cysteinyl leukotrienes in vivo.⁵² Additionally, the *S. aureus* exotoxin superantigen TSST-1 has been shown to augment antigen-specific IgE responses from atopic patients in vitro.⁵³

Patients with perennial allergic rhinitis to house dust mite had higher symptom scores if colonized nasally with *S. aureus*.⁵⁴ Further, colonization with known enterotoxin superantigen-producing strains was more likely in the allergic patients as compared with nonallergic controls. Allergic patients colonized with enterotoxin-producing *S. aureus* strains also had enhanced peripheral blood lymphocyte production of IL-4 and IL-5 in response to these superantigens in vitro. Although there were no differences in patient allergic symptom scores between those colonized with any of the then-known five *S. aureus* enterotoxin-producing strains analyzed compared with nonenterotoxin-producing *S. aureus* strains, all potential *S. aureus* enterotoxin-producing strains were not actually identified because new *S. aureus* enterotoxins are still being discovered. A total of 25 are now known, but recent whole-genome sequencing of methicillin-resistant *S. aureus* found evidence to suggest that the total potential heterogeneity of these superantigenic enterotoxins may be as large as the genetic diversity of all TCR V β and HLA class II molecules combined.³⁸

Alternaria, but not *Aspergillus*, *Penicillium*, or *Cladosporium*, has recently been reported to be a potent in vitro peripheral blood lymphocyte stimulant for IL-5, IL-13, and interferon- γ production from patients with HSD regardless of atopic status.⁵⁵ This effect was not seen in normal controls without HSD. *Alternaria* is a member of the dematiaceous mold family that includes *B. spicifera*, the most common AFS organism.²⁰ Virtually all dematiaceous fungi are capable of causing AFS, whereas *Penicillium spp.* and *Cladosporium spp.* have generally not; *Aspergillus spp.* AFS occurs but is much less common.²⁰ The fact that dematiaceous fungi predominate in AFS and are also capable of stimulating T

cell cytokine production from patients with HSD may be more than a coincidence. It suggests a relationship between HSD, AFS, and dematiaceous fungal-induced immune activation. It is possible then, that dematiaceous fungi such as *Alternaria* have potent T cell superantigenic activity, capable of binding common TCR V β motifs for superantigens if present in the host. Fungi are not usually seen from surgical sinus histopathology or surgical sinus cultures in non-AFS HSD unless the patient has another form of fungal sinusitis. Because various microbial superantigens are capable of binding to the same or similar TCR V β motifs,^{29,31,32} it is possible that putative *Alternaria* superantigen activity in vitro may be acting in this study as a surrogate for the presence of an intrasinus microbial superantigen that is the actual HSD etiologic agent, such as *S. aureus* enterotoxin. This is supported by the recent finding of anti-SEB and dematiaceous fungal IgE in situ in HSD nasal polyps.³ If this theory is correct, HSD patients should carry common TCR V β motifs capable of binding relevant microbial superantigens. Further, these motifs may be similar for both SEB and putative dematiaceous fungal superantigen-binding because specific IgE to both were virtually always seen together.³

A recent report has shown that antigen-specific T cell lines established from ABPA patients by stimulation in vitro with the immunodominant *A. fumigatus* antigen Asp f1 carry primarily the TCR V β 13 motif.⁵⁶ However, similar T cell lines from patients with type I immediate hypersensitivity to *A. fumigatus* who had either asthma or cystic fibrosis, but did not have ABPA, were found not to carry TCR V β 13; these non-ABPA T cell lines preferentially carried TCR V β 1 instead. TCR V β 13 is a common microbial TCR superantigen-binding motif, whereas TCR V β 1 is not.^{29,31,32,49} One possible conclusion is that the protection against ABPA seen in *A. fumigatus* allergic non-ABPA patients is attributable to lack of *A. fumigatus* superantigen TCR-binding capability by Asp f

1-specific T cells carrying the putative nonsuperantigen-binding TCR V β 1. This might prevent subsequent superantigen-induced T cell activation that, in concert with antigen-specific Asp f 1 TCR recognition (and probably other antigen-specific and nonspecific immune events), might be required to produce clinical ABPA. One potential candidate for this superantigen is Asp f 1 itself.

Another potential superantigen candidate is Asp f 4, an *A. fumigatus* allergen with unknown function. It induces a significant antigen-specific IgE response in ABPA patients, but not in other *A. fumigatus*-allergic patients; it has a specificity for ABPA of 100% and sensitivity of 90%.⁵⁷ It is tempting to speculate that this is a T cell superantigen for ABPA, analogous to *S. aureus* enterotoxin in atopic dermatitis. Further studies to test this hypothesis will be required.

T Cell Superantigen Theory for the Pathogenesis of HSD, AFS, ABPA, and Severe Asthma

It is possible that many patients with HSD have microbial T cell superantigen production within the sinus cavities, with subsequent sinus mucosal immune activation in a genetically susceptible host underlying the pathogenesis of the disorder. Such superantigen-induced immune activation could play upon and amplify antigen-specific and associated immunopathologic effects. This is testable by prospectively looking for associations between surgical sinus microbial culture results, enterotoxin or other superantigen production, and clinical, immunologic, and histopathologic parameters. Likely candidates for superantigen-induced HSD include enterotoxin-producing strains of *S. aureus*, primarily because patients with HSD and AFS are often culture-positive,^{20,25} patients with HSD commonly have in situ anti-SEB IgE that correlates with the presence of both IL-5 and eotaxin,³ and *S. aureus* enterotoxin production is common and capable of producing the type of inflammation seen.⁵¹ However, other extracellular and intracellular bacteria,

specific fungi (particularly dematiaceous), or persistent viruses including retroviruses, alone or in combination, may be etiologic in individual cases. Additionally, TCR V β analysis of in situ sinus mucosal T cells in HSD, as has been reported in atopic dermatitis⁴¹ and asthmatic BAL,⁴⁹ should show preferential recruitment of T cells with a restricted heterogeneity of TCR V β motifs that are capable of binding relevant microbial superantigens. Animal models can be tested to evaluate the ability of specific superantigens to induce HSD with or without concomitant antigen-specific immune responses.

What else could be predicted from the superantigen theory of HSD and related respiratory disorders? HSD and AFS patients should carry the proper TCR V β motifs for relevant microbial superantigen-binding. Organisms with superantigenic potential should be the most common microbes cultured from close proximity to the respiratory mucosa. Dematiaceous fungi should prove to have superantigenic potential compared with other fungi. Dematiaceous fungal or *A. fumigatus* superantigen-dependent immune activation should be required for the production of AFS or ABPA, respectively. *A. fumigatus* should have superantigenic properties in ABPA patients, who should carry the proper TCR V β motifs for *A. fumigatus* superantigen(s). Alternatively, the co-presence of other microbial superantigens, such as *S. aureus* enterotoxin or retroviral envelope glycoprotein, might be required in some or all of these patients. Superantigen-induced immune activation would help to explain why these analogous disorders produce high polyclonal total serum IgE levels with associated intense eosinophilic-lymphocytic mucosal tissue inflammation that could be considered disproportionate to the physical numbers of fungi present within the allergic mucin as analyzed by fungal stains on surgical mucosal histopathology.^{20,23} This would also be consistent with the report that more, rather than less, mucosal resective sinus surgery in AFS leads to improved clinical responses to medical management postoperatively.^{20,23,58} Such

surgery would presumably be more effective in the physical removal of mucosa-associated superantigen-producing microbes. The putative role for *Mycoplasma*, *C. pneumoniae*, or persistent viruses in the pathogenesis of chronic asthma might also be explainable based on superantigen activity. *Mycoplasma* and human retroviruses have already been shown to have superantigenic activity.^{30,34–36} Further, it is possible that this inflammatory mechanism is fundamentally important for many other chronic diseases. This may include type I diabetes, multiple sclerosis, and common forms of connective tissue diseases such as rheumatoid or reactive arthritis because microbial superantigens have been either implicated or isolated from the target organs of these diseases.^{35,36,47,48}

Superantigen-responsiveness might be necessary but not sufficient for AFS and ABPA pathogenesis because both are correlated with the presence of antigen-specific IgE and IgG responses. They are also correlated with the presence of selective HLA class II molecule phenotypes on APC.^{59,60} The association of selective HLA class II phenotypes with both AFS and ABPA may relate to a combination of classic HLA class II molecule peptide antigen presentation constraints and class II molecule superantigen-binding because some class II molecules and their subtype alleles show preferential binding for specific superantigens.³² Taken together, preexisting type I immediate hypersensitivity, other antigen-specific immune responses, TH1/TH2 cytokine

dysregulation, leukotriene dysregulation, proper genetic mutations, and other pathology may be important constituents in the etiology of all the disorders discussed, with various individuals carrying a heterogeneity of such factors. However, these factors may serve as preamplification signals that create immunopathology which becomes amplified through superantigen-induced T cell stimulation in the host to generate the intensity and chronicity of inflammation that produces the clinical disorder (Fig 3.)

Such amplification could explain the finding of higher mean polyclonal total serum IgE, fungal-specific IgE, fungal-specific IgG levels, and eosinophilia in ABPA in comparison with AFS.²⁰ Whereas the reason(s) for these differences might include organ-specific and other host-determined factors, differences in the properties of the putative superantigens produced by the two unrelated families of fungi (*Aspergillus spp.* vs dematiaceous fungi) may be involved. These could include inherent differences in superantigen-dependent T cell stimulation capability. The recent finding that increased in situ total and allergen-specific IgE levels, IL-5, and eotaxin all correlate with the co-presence of anti-SEB IgE in HSD³ would be expected based on the superantigen model presented. Further, superantigen responsiveness might be applicable to the findings that respiratory arrest in children and young adults with asthma correlates with *Alternaria* exposure in the midwest,⁶¹ and the

PROPOSED MODEL FOR SUPERANTIGEN-INDUCED CHRONIC INFLAMMATORY DISORDERS

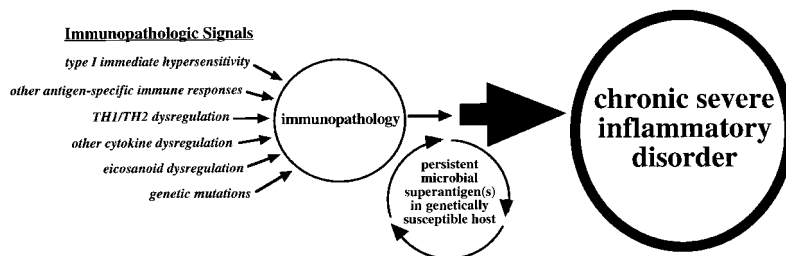


Figure 3. Proposed model for the creation of chronic severe inflammatory disease by microbial superantigens. A potential heterogeneity of immunopathologic signals create immunopathology which is amplified through T cell stimulation by persistent superantigen(s) in the genetically susceptible host resulting in the final clinical disorder.

presence of *Alternaria* allergy in young children from the southwest who wheeze is prognostic for persistent asthma.⁶²

None of the chronic eosinophilic-lymphocytic respiratory mucosal inflammatory disorders presented have been shown to be responsive to antimicrobial therapy in any meaningful way. This is not unexpected given the noninvasive nature of the extracellular bacterial and fungal processes and the persistent nature of obligate intracellular organisms such as *C. pneumoniae* or retroviruses. Such microbes are currently either difficult or impossible to eliminate. The presence of the etiologic extracellular microbes may be analogous to the carrier state for nasal *S. aureus*, where host epithelial cell surface molecules facilitate microbial binding and persistence.⁵⁴ It is well known that nasal *S. aureus* carriage is generally refractory to systemic antimicrobials; even with adequate topical therapy it carries a 50% recurrence rate.⁶³ Chronic viral protein exposure would be expected from etiologic persistent viruses, allowing long-term contact with putative viral superantigens. In general, specific mucosal factors that allow microbial colonization and persistence such as functional or anatomic mucociliary transport obstruction which can be induced by an initial inflammatory injury, together with the proper display of epithelial cell microbial binding proteins, may be required of the host as an initial step in disease development. A combination of factors that include both local superantigen production and persistence, together with genetically determined host responsiveness would be necessary to allow superantigen-induced eosinophilic-lymphocytic inflammatory respiratory mucosal disease to develop in the first place.

Proof for a fundamental role for superantigen activity in any of these respiratory disorders would cause a paradigm shift in our understanding of their biologies with attendant consequences for future treatment strategies. Identification and permanent removal or neutralization of the offending su-

perantigen(s) might lead to significant clinical improvement or even resolution of the disorder. For example, it may be possible to block SEB superantigen activity with a bispecific receptor mimic specific for HLA class II and TCR V β SEB superantigen-binding motifs.⁶⁴ Additionally, identification of epithelial or other mucosal factors that are fundamental to the persistence of relevant microbes might allow the development of treatments to counteract these factors. Patients at high risk for the acquisition of these disorders might be identified early, possibly allowing effective preventive treatment.

CONCLUSION

Multiple lines of evidence now point toward a unifying theory for the etiology of HSD and clinically associated disorders. This theory predicts that the local presence of microbial superantigens as immune activators in the proper host is essentially involved in the development of chronic eosinophilic-lymphocytic respiratory mucosal inflammation, particularly the rhinosinusitis disorders HSD and AFS, and severe asthma including variants such as ABPA. Type I immediate hypersensitivity and other immunopathologic signals, when present, may be important factors in the pathogenesis of all these related disorders. Such factors would lead to immunopathology that becomes amplified into the clinical disorder through the action of local superantigen(s). Specific superantigens have already been shown capable of producing the type of inflammation seen. Other than that associated with putative superantigen-producing obligate intracellular microbes such as persistent viruses or intracellular bacteria, true mucosal-invasive infection as etiologic in any of these disorders seems unlikely from a clinical and histopathologic viewpoint. An important role for superantigens in atopic dermatitis has already been proven, and current research is consistent with superantigen theory in severe asthma. Further studies will now be needed to conclusively prove that superantigens play an important role in all of these

related conditions. Fundamental changes in our understanding of pathophysiology and future treatments for these common disorders will occur if this hypothesis proves true.

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CME Examination

1–5, Schubert MS. 2001;87:181–188.

CME Test Questions

1. Patients with chronic hypertrophic sinus disease can be described as having:
 - a. Microabscesses on mucosal histopathology.
 - b. Recurring cycles of inflammatory sinonasal mucosal hypertrophy and hyperplasia.
 - c. Granulomatous mucosal changes when allergic fungal sinusitis predominates.
 - d. In situ mucosal T cell cytokine profiles in common with many partial immunodeficiency syndromes.
 - e. Concomitant asthma dependent upon microbial antigen-antibody complexes.
2. For biologic activity, T cell superantigens require:
 - a. Classical antigen presentation by HLA class II molecules on APC.
 - b. Proper HLA class II α 2 region genetics.
 - c. Proper TCR V region hyper-variable mutations.
 - d. Proper TCR V β region genetics.
 - e. Dysregulation of T cell cytokine profiles.
3. The following have been found when comparing chronic hypertrophic sinus disease and chronic severe asthma, EXCEPT:
 - a. The concept of “allergic” and “nonallergic” patients no longer applies.
 - b. The microbes most commonly implicated have been shown to produce T cell superantigens.
 - c. The presence of associated diseases characterized by fungal hypersensitivity.
 - d. As the severity of hypertrophic sinus disease increases by radiographic parameters, the incidence of asthma increases.
 - e. Similarities in in situ mucosal or BAL T cell cytokine profiles.
4. TRUE/FALSE. The following microbes have been shown to produce T cell superantigens:
 - a. — Retroviruses.
 - b. — Epstein-Barr virus.
 - c. — *Mycoplasma*.
 - d. — *Staphylococcus aureus*.
 - e. — *Cladosporium spp*.
5. TRUE/FALSE. Comparing allergic fungal sinusitis and allergic bronchopulmonary aspergillosis:
 - a. — Mean total serum IgE levels in allergic fungal sinusitis and allergic bronchopulmonary aspergillosis are elevated but dissimilar in magnitude.
 - b. — *Aspergillus spp.* are the primary etiologic fungi in both.
 - c. — Specific IgE to the etiologic fungal organism seems necessary but not sufficient for disease persistence.
 - d. — Current research indicates HLA class II phenotypes may play an important role in disease pathogenesis.
 - e. — In situ TCR V β motifs are known to be similar.

Answers found on page 210.