Introduction

Recent expert panels have defined chronic rhinosinusitis (CRS) as a clinical syndrome rather than a discrete disease entity, with emphasis on chronic inflammation rather than infection [1]. In the past CRS was believed to be secondary to anatomic abnormalities leading to ostial obstruction and/or persistent bacterial infection. Symptomatic recurrence of CRS despite adequate surgery, however, resulted in general acceptance of the concept that no one causative factor can fully explain the clinical heterogeneity and pathologic manifestations of the condition. There is growing consensus toward the concept that CRS results from multiple factors that may be working simultaneously or independently in an individual patient. Potential contributing sources can be categorized into: host factors, including anatomic abnormalities, allergy, immune dysfunction, mucociliary defects, metabolic perturbations, such as aspirin intolerance; and environmental factors including micro-organisms, biofilm formation, osteitis, fungal colonization associated with eosinophilia, and bacterial superantigens. The focus of this chapter will be on the hypothesized role of bacterial superantigens (SAg) in CRS with nasal polyps.

Chronic rhinosinusitis is commonly classified into CRS without polyps (CRSsNP) and CRS with polyps (CRSwNP) with SAg playing a proposed role thus far only in the latter. Overall, CRS affects approximately 15% of the American population [1], while CRSwNP occurs in about 20% of those patients with CRS [2]. Patients with polyps represent a distinct group that is clinically more symptomatic and particularly refractory to both medical and surgical therapy. CRSwNP is frequently linked to steroid-dependent asthma and aspirin intolerance. The most common pathology of the sinus mucosa in CRSwNP is similar to that seen in the bronchial mucosa of asthmatics, infiltrates consisting mainly of lymphocytes, plasma cells, and eosinophils. Histologically, nasal polyposis is characterized by a chronic eosinophilic inflammatory pattern in 70–90% of cases [3], tissue edema, and local IgE production. Histologic findings in CRSsNP in general reveal much less tissue eosinophilia and edema with more prominent glandular hyperplasia [4]. The above division of CRS into eosinophilic CRSwNP and relatively non-eosinophilic CRSsNP is somewhat artificial, since polyps with minimal tissue eosinophilia exist in both cystic fibrosis and...
polyps from Southeast Asia [5, 6]. Nevertheless, despite these exceptions, the triggers for eosinophil recruitment and activation are believed to play a central role in the development of polyps in the vast majority of cases.

Once thought to be an eosinophilic inflammation of allergic origin, evidence has accumulated against allergy in the pathophysiology of nasal polyposis [7]. Furthermore, recent studies have demonstrated that colonization of the nasal cavity with *Staphylococcus aureus* is much more frequent in CRSwNP patients than in those without polyps, suggesting that these bacteria might play a role in the formation of polyps [8]. *S. aureus* is a common microbial agent that is known to release staphylococcal enterotoxins (SE), which act as superantigens (SAg), allergens, and conventional antigens, playing important roles in the development, amplification, and maintenance of the mucosal inflammation in CRSwNP.

### What Are Superantigens?

Superantigens are proteins of microbial or viral origin known for their potent lymphocyte-transforming (mitogenic) activity toward human T lymphocytes. Microbial SAg are powerful modifiers of the immune system, which may result in massive T-cell activation, cytokine release, and in some cases systemic shock. SAg are able to trigger excessive and aberrant activation of T cells by bypassing the normal antigen processing step. As depicted in Fig. 19.1, during a conventional response, an antigen is recognized and processed within an antigen processing cell (APC). Peptide fragments of the processed antigen are displayed in the peptide binding groove of the major histocompatibility complex (MHC) class II molecule on the surface of the APC. These fragments are presented to surrounding T lymphocytes. Only those CD4+ T cells that recognize the MHC class II molecule with the bound peptide fragment will be stimulated. This is an extremely specific response that activates only a tiny fragment of the host T cell population (less than 0.01%) [9, 10]. In contrast, SAg bind as intact molecules to a region outside the peptide binding groove of the MHC class II molecule (Fig. 19.1). SAg stimulate both CD4+ and CD8+ T cells in an MHC II-dependent manner; however, T cell receptor (TCR) recognition is not MHC-restricted [11]. Binding to the MHC class II molecule outside the antigen-binding groove prevents the TCR from having cognate recognition of the surface of the MHC molecule, which would be required for usual antigen presentation. SAg bind to the V-beta domain of the TCR and any T cell bearing the appropriate V-beta type will be stimulated by the SAg regardless of the MHC allotype. It is the bridging of the TCR and the MHC class II molecule that leads to massive proliferation and release of cytokines, chemokines, and adhesion molecules, T cell activation, activation-induced apoptosis and anergy [12]. In contrast to the conventional antigen response, which activates less than 0.01% of the host T-cell population, SAg may activate up to 25% [13]. Concentrations of less than 0.1 mg/mL of the bacterial SAg may be enough to stimulate an uncontrolled T cell response, leading to systemic collapse, shock, and death [14].

### Staphylococcal Superantigens

To date the most extensively studied SAg are exotoxins produced by the Gram-positive bacteria *S. aureus* and *Streptococcus pyogenes*, organisms commonly found on the skin, in the nose, and in the upper respiratory tract of humans. The number of staphylococcal and streptococcal SAg is evolving as genome sequencing databases grow. As of 2003, 32 staphylococcal and streptococcal SAg have been discovered [15]. The focus of this chapter will be on SE, the SAg that have been linked to CRS, including staphylococcal exotoxins A-Q (SEA-SEQ) and toxic shock syndrome toxin-1 (TSST-1). These are heat-stable proteins ranging from 22.5 to 28 kDa in molecular weight. Overall, these proteins share significant nucleotide and amino acid sequence homology ranging from 32 to 82% and from 21 to 82% respectively [16]. Despite differences in primary amino acid sequencing, the toxins appear as compacted ellipsoidal proteins sharing a common characteristic two-dimensional folding pattern [17, 18]. Despite a highly conserved structural fold, individual bacterial SAg have evolved different mechanisms of binding to MHC class II molecules and TCR. It is likely that staphylococcal and streptococcal SAg have evolved from a single primordial superantigen. The evolution of SAg indicated that for at least some microbes, these toxins confer an advantage and may be an important mechanism for survival.

### MHC Class II Binding

As discussed above, SAg bind as intact proteins, directly to the MCH class II molecule outside of the peptide binding groove. SAg have developed three basic mechanisms for binding to the MHC class II molecule [19]. They may bind to a single alpha chain (e.g., SEB), a single beta chain (e.g., SEH) or they may bind and crosslink two MHC class II molecules [20]. Some SAg, like SEH, require a zinc ion to effectively bind the MHC class II molecule [21]. In addition, the affinity of SAg toward different MHC class II isoforms and alleles varies considerably and appears to influence SAg potency [22]. It is thought that SAg recognition by certain T cells is strongly influenced by polymorphic residues of the MHC class II molecule [23]. In humans, the MHC class II molecules can be divided into HLA DR, DQ, and DP isoforms. While in humans, HLA-DR is the predominant MHC class II receptor for most SAg, some appear to have a higher binding affinity for HLA-DQ (Table 19.1) [24]. For example, most staphylococcal exotoxins bind HLA-DR preferentially, whereas many streptococcal pyrogenic exotoxins bind better to HLA-DQ. It has been well established that the MHC polymorphism influences individual SAg activity. Kotb and colleagues showed that certain HLA haplotypes conferred strong protection from severe systemic disease caused by invasive streptococcal infection, whereas other haplotypes increased the risk of severe disease [25]. This may explain why some individuals appear to be relatively protected from the lethal effects of SAg.