Symposium 1: Immunity and pathogenesis of AR and CRS

Superantigens and upper airway diseases

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Introduction

Superantigens (SAgs) are a class of bacterial and viral antigens which may trigger non-specific polyclonal T cell activation and massive cytokine release.[1] The best characterized are staphylococcal enterotoxins (SEs) and streptococcal pyrogenic exotoxins that cause staphylococcal and streptococcal toxic shock syndromes. Unlike conventional antigens, SAgs can directly bind to the lateral aspects of the MHC class II molecule and to the T-cell receptor (TCR). Binding site on the TCR is the variable region of the beta chain (the V β region); since the number of different V β regions in the human T-cell repertoire is restricted to less than 50 and most SAgs can bind more than one, SAg can activate up to 20～25% of the body's T-cell repertoire. This superantigenic capability is in marked contrast to conventional antigen, as the latter can activate only a tiny fraction of the host's T-cells (0.0001～0.001%).[2]

It is a matter of question why the microbes have acquired and produce SAgs. However, considering the fatal consequences of systemic toxic shock syndromes, massive injury to host would not be the original purpose. As the induction of T-cell anergy is another effect of SAgs[3], it is tempting to speculate that the trace level secretion might facilitate the colonization and survival.

Staphylococcal superantigens in upper airway diseases

Staphylococcus aureus (SA) is a common human pathogen but is also a frequent colonizer in the nasal mucosa, the skin and the intestinal tract. The anterior nares are the most frequent site for the bacterial colonization and about 30～40% of general population are the nasal carriers.[4,5] Of note, nasal SA

colonization rates are frequently elevated in patients with upper airway diseases than in controls. In a study of patients with perennial allergic rhinitis, the nasal carriage rate was higher in the patient group (44%) than in the control (20%).[6] Chronic rhinosinusitis with nasal polyps (CRSwNP) may be more relevant to the bacteria, as SA colonization rate was significantly elevated in CRSwNP patients (60% of CRSwNP and 87% of CRSwNP with comorbid asthma and aspirin sensitivity), than in controls (33%).[7] In addition, IgE antibodies specific to staphylococcal enterotoxins (SE-IgE) were present in 28% of local tissue samples, with rates as high as 80% in the subgroup of CRSwNP with comorbid asthma and aspirin sensitivity, which was also significantly higher than 15% in controls.[7] A recent metagenomic study of nasal lavage fluids demonstrated that microbial diversity was reduced in CRSwNP but SA and its secreting extracellular vesicles were particularly more prevalent in the samples from CRSwNP compared with CRS without polyps (CRSsNP).[8]

Associations of staphylococcal superantigens with asthma

Relevance of staphylococcal SAgs may extend to the risk of asthma in susceptible individuals. Nasal SA colonization rates showed positive relationships with asthma prevalence and/or activity markers in general adult populations.[9,10] The associations were stronger in patients with CRSwNP than those with CRSsNP, suggesting the potential that nasal inflammatory status may be a gateway by which nasal SA influences the lower airways or host system.[7,11] In addition, a recent study of inner-city adolescents in the US suggested that home environmental exposure to staphylococcal SAgs may contribute to asthma activity.[12]

Meanwhile, serum SE-IgE levels, which is a systemic marker for the bacterial exposure, had significant relationships with asthma prevalence in general adult population studies.[13,14] Furthermore, the specific IgE levels were positively associated with asthma severity in adults, and the sensitization was specifically related to late-onset severe asthma comorbid with CRSwNP.[15,16] In a multi-center cohort study of patients with chronic rhinosinusitis, the clusters with comorbid asthma were characterized with high local levels of IL-5, total IgE and SE-IgE.[17] These findings collectively led to the idea that staphylococcal SAgs may act like allergens and link upper and lower airway conditions.

Mechanistic roles of staphylococcal superantigens in airway diseases

As SA is frequently localized in the nasal mucosa but not in the lower airways, its direct effects may need to be interpreted in the context of upper airway diseases. In the literature, effects of staphylococcal SAgs on airway diseases were mostly focused on staphylococcal enterotoxin B (SEB). In a mouse model of ovalbumin-allergic asthma, intranasal instillation of low-dose SEB facilitated the allergic sensitization and consecutive development of eosinophilic airway inflammation.[18] In an experimental allergic rhinosinusitis

murine model, SEB induced nasal polypoid lesions, in combination with ovalbumin exposure.[19] Allergenic functionality of SEB (to induce mast cell or basophil degranulation) has been documented in samples of patients with nasal polyps or chronic urticaria.[20,21]

A recent series of studies discovered novel bacterial allergens, staphylococcal serine protease-like proteins (Spls) in humans and mice.[22,23] Spls were identified as dominant IgG4-binding SA proteins in the plasmas of SA carriers and Spl-specific IgE levels were significantly increased in patients with asthma.[22] Intra-tracheal administration of Spl-D could induce IgE sensitization and allergic asthma in an IL-33 dependent manner.[23] Proteomics studies may identify further pro-allergic roles of staphylococcal antigens.

Summary

SA has gained scientific interests following the identification of associations between this pathogen and various allergic diseases. Recent evidence indicates that staphylococcal SAgs may have major roles in severe or refractory allergic airway diseases including asthma and CRSwNP. Recent discovery of novel staphylococcal proteins and toxins may open a new field to manage the SA-related allergic airway diseases. Given the chronic nature of allergic diseases and a variety of SAgs produced by SA, their exact roles may warrant comprehensive investigation from epidemiological and molecular perspectives.

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