



Short review

Staphylococcus Aureus in chronic airway diseases: An overview

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ABSTRACT

This review investigates about the role of Staphylococcus Aureus (*S. aureus*) and *S. aureus* enterotoxins (SEs) in the pathogenesis of several chronic airway diseases. *S. aureus* is part of normal human flora and may colonize the skin and the upper airways. SEs acting as superantigens can induce an intense T cell activation and through the release of interleukin (IL) - 4, 5, and 13, can promote a polyclonal IgE response and eosinophilic inflammation. *S. aureus* can damage epithelial cells inducing the release of the so-called "alarmins" responsible of the activation of Type 2 innate lymphoid cells (ILC-2) linked to an IL-5 mediated airway eosinophilic inflammation. SEs sensitization has been recently associated with the eosinophilic endotypes of both nasal polyps and late onset severe asthma. Studies investigating the effect of biological therapies in SEs sensitized patients should be performed in order to better define the role played by *S. aureus* in the different endotypes of severe asthma and/or chronic rhinosinusitis.

1. Introduction

Chronic airway diseases encompass a broad spectrum of upper and lower airway disorders such as rhinitis, chronic rhinosinusitis, bronchial asthma, and chronic obstructive pulmonary disease (COPD), that frequently co-occur because they can represent different manifestations of a single underlying pathobiological process [1]. The pathogenesis of these disorders includes the interaction between the subject genetic background and external stimuli resulting in activation of pro-inflammatory pathways. A growing body of researches have showed that infectious agents may influence the onset and the clinical behavior of several atopic and non-atopic diseases.

Staphylococcus Aureus (*S. aureus*) frequently colonizes the skin and upper airways, and can secrete staphylococcal enterotoxins (SEs) that, acting as superantigens, may induce an intense polyclonal T cells proliferation and activation. Through T cell release of interleukin (IL)-4, IL-5 and IL-13, SEs can enhance class switching to IgE and eosinophilic inflammation. Furthermore, *S. aureus* can damage epithelial cells inducing the release of the so-called "alarmins" that can activate type 2 Innate Lymphoid Cells (ILC-2) contributing to eosinophilic inflammation and airway remodeling, through the synthesis of IL-5 and IL-13.

Epidemiologic studies that have investigated the prevalence of SEs sensitization in community-based populations [2–5], demonstrated that smoking history, male sex, older age (≥ 61 years), and sensitization to

inhalant allergens are the main risk factors. Recently, several researches about the role of *S. aureus* and SEs revealed their pathogenetic role in several endotypes of chronic rhinosinusitis with nasal polyposis and severe asthma. In this review, we examined the main microbiological aspects of *S. aureus* and the current knowledge about the biological role of *S. aureus* in the pathogenesis of chronic airway disorders.

2. Staphylococcus Aureus

S. aureus is a nonmotile, Gram-positive, catalase-positive, not forming spores, and facultative aerobic-anaerobic bacterium. It is a member of the normal human flora and often colonizes the skin and the upper respiratory tract. The anterior nares provide the main habitat for *S. aureus* that can commonly be found as a commensal; 20–25% of the population is persistently colonized by *S. aureus* and 60% is an intermittent carrier [6–8].

S. aureus is able to form a biofilm, composed by a hydrated matrix of polysaccharides and proteins, which provides cell adhesion. Adherent biofilms, particularly in nasal polyps, may facilitate the survival of *S. aureus* due to a defective epithelial barrier unable to remove bacterial colonization. *S. aureus* can replicate within nasal polyps' epithelial cells, invade the mucosa, and release chemical mediators that contribute to inflammation [9].

Over 70% of isolated *S. aureus* strains secrete a family of structurally

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related exotoxins, including toxic shock syndrome toxin-1 (TSST-1) and the SEs serotypes SE-A, SE-B, SE-C, SE-D, SE-E, and SE-G, which are potent T-cell superantigens.

In contrast to conventional antigens, superantigens do not require processing and antigen presentation by antigen-presenting cells (APC); they bind directly to the variable β -domain of the β -chain of the TCR molecule (TCRV β), interacting with the framework regions on T cells, and to the MHC class II on the surface of APC, outside the peptide-binding groove. This results in the activation of polyclonal T cells and in an excessive production of T cell cytokines including IL-4, IL-5 and IL-13. IL-5 is responsible of eosinophilic inflammation, while IL-4 and IL-13 induce B cell activation and class switching to immunoglobulin E (IgE), promoting a local polyclonal IgE response that may be reflected by an increase in total serum IgE levels. SEs can also behave as allergens inducing the production of specific IgE by mucosal B cells [10]. In the same way, recent evidences suggest that SEs may act on B cell as superantigens, interacting with IgE molecules through framework regions [11]. It is unclear whether these locally formed polyclonal IgE induced by SEs are functional, i.e. capable of binding to Fc ϵ receptor I on mast cells and basophils and activating them. It has been speculated that these IgE with so many different specificities may compete for the IgE-binding sites on mast cells preventing the cross linking of IgE [12]. On the contrary, recent studies suggest that IgE to SEs are functional. In patients with atopic dermatitis, Leung demonstrated that their own basophils isolated from the peripheral blood induced the release of histamine on exposure to the specific SEs, which they are sensitized to [13]. Zhang showed that mucosal tissue polyclonal IgE from nasal polyps are able to activate mast cells upon allergen challenge not only with typical inhalant allergens but also with SE-B, although specific IgE Abs to SEs in nasal polyps tissue could be found independently of their presence in serum [14].

Although SEs mainly affect the activation of lymphocytes, several studies have investigated the effects of SEs on other inflammatory cells, such as eosinophils, macrophages, and mast cells. It has been shown that SEs may promote eosinophils survival by inhibition of eosinophil apoptosis [15]. Further, SEs can act on macrophages inducing the production of cytokines such as IL-8 and IL-12 [16,17], and neutrophilic chemotactic factors [18]. Regarding mast cells, *S. aureus* protein A can induce cross-linking of IgE molecules leading to an increased release of histamine, tryptase and leukotriene C4 [19].

S. aureus, as well as other stimuli such as virus and air pollutants, may influence type 2 responses not only via the production of enterotoxins, but also through the activation of ILC2. In fact, it has been demonstrated that *S. aureus* can induce the epithelial cells to release IL-25, IL-33 and thymic stromal lymphopoietin (TSLP). These so called “alarmins” can act on ILC2 inducing the production of type 2 cytokines, including IL-5 linked to the eosinophilic inflammation. This pathogenetic mechanism has been shown in different experimental models and clinical studies. Heat inactivated *S. aureus* increased IL-33 production in human and murine epidermal keratinocytes and murine dermal macrophages [20]. Higher levels of IL-33 have been detected in atopic dermatitis mouse model after SE-B exposure [21]. Higher production of TSLP has been shown in patients with perennial allergic rhinitis sensitized to SEs [22]. Recently, Nagarkar documented that the biological activity of cleaved TSLP is increased in CRS with nasal polyps [23]. Finally, Lan demonstrated, for the first time, that non-producing enterotoxin strains of *S. aureus*, but not of staphylococcus epidermidis, directly induce the release of epithelial cell-derived IL-33 and TSLP [24]. Type 2 polarization induced by *S. aureus* and its enterotoxins can allow the long-term survival of the bacteria through the activation of the “so called” M2 macrophages characterized by a decreased phagocytosis of *S. aureus* [25].

Although the first data on the involvement of *S. aureus* in the pathogenesis of atopic diseases were obtained in patients affected by atopic dermatitis, more recent studies have closely related *S. aureus* to the pathogenesis of several airway diseases.

3. *S. aureus* and allergic rhinitis and chronic rhinosinusitis

S. aureus colonization is more frequent in patients affected by perennial allergic rhinitis with rates of 44% versus 20% in control subjects [26]. Allergic *S. aureus* carriers have higher symptom nasal scores and the sensitization status to SEs seems to be related to the clinical severity of allergic rhinitis, as shown by higher levels of serum eosinophilic cationic protein (ECP) [27,28].

Chronic rhinosinusitis (CRS) is a heterogeneous group of inflammatory diseases of the nasal and paranasal cavities that is usually classified according to the presence (CRSwNP) or absence (CRSSNP) of nasal polyps (NP) [29]. CRSwNP and CRSSNP show different mucosal remodeling and inflammatory patterns, comorbidities, response to therapy and rate of recurrence after surgery. Fibrotic mucosa and basement membrane thickening, goblet cell hyperplasia and mild cellular infiltrate with the transforming growth factor (TGF)- β playing a central role in the remodeling process [30], characterize CRSSNP; CRSSNP has mainly a Th1/Th17 inflammatory profile with a predominant neutrophilic infiltration [31]. In comparison with patients affected by CRSwNP, those with CRSSNP have a lower rate of asthma and aspirin exacerbated respiratory disease (AERD) comorbidities and a lower recurrence after surgery [32]. Conversely, CRSwNP is characterized by an intense edematous stroma and inflammatory cell infiltration, low TGF- β expression associated with a deficit of T regulatory cells [30,31]. It has been suggested that the deficit of T regulatory cells may account for the stronger inflammatory process in CRSwNP [31]. Different inflammatory patterns (i.e. predominantly eosinophilic or neutrophilic) regulated by different T helper cell populations, (i.e. Th1, Th2 or Th17 cells) has been described in CRSwNP patients, probably related with a different geographical/racial distribution. In fact, more than 80% of Caucasian CRSwNP patients express a Th2 profile with eosinophilic infiltration and high levels of IL-5 expression. This inflammatory profile has been described in less than 20% of Chinese CRSwNP patients, who usually show a noneosinophilic, frequently neutrophilic inflammatory pattern, with a Th1/Th17 immune profile [33]. Asthma comorbidity is significantly higher in Caucasian CRSwNP patients compared to the Asiatic counterparts. The different inflammatory pattern in the Caucasian and Asiatic CRSwNP patients may be related with a different rate of nasal *S. aureus* colonization. In particular, < 5% of Asiatic CRSwNP patients is colonized by *S. aureus*; on the contrary, higher rates of *S. aureus* colonization, ranging from 67 to 87%, have been identified in European CRSwNP patients [34]. In mucosal tissue samples of nasal polyps obtained from Caucasian patients, Bachert showed a higher rate of IgE against SEs (37%) compared to Chinese CRSwNP patients (17%). In both groups, SE-IgE positivity was associated with increased total IgE, ECP, IL-5 concentrations and asthma comorbidity, suggesting a role of *S. aureus* in amplifying Type 2 inflammation [33]. The role of *S. aureus* superantigens in the pathogenesis of CRSwNP has been further confirmed by a meta-analysis that demonstrated a higher detection of *S. aureus* positive culture, SEs and their specific IgE in the CRSwNP group in comparison with the control group [35].

Recently, Tomassen performed a cluster analysis in a subset of the European multicenter case control study group (GA2LEN sinusitis cohort) consisting of 173 CRS patients and 89 control subjects. They analyzed the tissue expression of cytokines and other biomarkers associated with different T cell subsets (Th1, Th17, Th22 or Th2) and evaluated their relationship with phenotype features such as nasal polyposis and asthma comorbidity. They classified RSC patients in 10 clusters. The first four clusters were characterized by low or undetectable IL-5, immunoglobulin E (IgE), and ECP: among these, three clusters clinically resembled CRSSNP without asthma comorbidity, and one cluster showing a Th17 profile had mixed CRSSNP/CRSwNP. The latter six clusters were characterized by moderate to high IL-5 expression and were in turn classified into two groups: the first group with moderate IL-5 production, increased asthma prevalence and mixed

Table 1
SEs-IgE and asthma.

Author	Study population	Mean age (yr)	SEs-IgE Cut off	SEs-IgE association with asthma	SEs-IgE association with markers of asthma severity
Semic-Jusufagic, 2007 [5]	510 subjects	0 (follow up for 5 years)	SEs mix (SE-A, SE-C, TSST-1) > 0.35 kU/L	Current wheeze OR: 1.90 (95% CI: 1.00–3.60; p = 0.05)	↑ Airway hyperresponsiveness
Tommasen, 2013 [2]	2908 subjects	48.9	SE-A, SE-C, TSST-1 > 0.01 kU/L	Asthma OR: 2.10 (95% CI: 1.60–2.76; p = 0.001)	
Song, 2014 [3]	1080 subjects	60.2	SEs mix (SE-A, SE-C, TSST-1) ≥ 0.35 kU/L	Current asthma OR: 2.52 (95% CI: 1.36–4.67, p = 0.003) Adult-onset current asthma OR: 2.46 (95% CI: 1.34–4.54, p = 0.004)	
Lee, 2006 [38]	80 Aspirin intolerant asthma 62 Aspirin tolerant asthma 52 Controls	41.1	SE-A, SE-B, TSST-1 ≥ 0.35 kU/L		↑ Airway hyperresponsiveness
Kowalski, 2011 [40]	109 Severe refractory asthma 101 Non severe asthma 45 Controls	42.4	SEs mix (SE-A, SE-C, TSST-1) ≥ 0.01 kU/L	Severe asthma OR: 1.94 (95% CI: 0.995–3.788; p = 0.052)	↓ FEV ₁ , FEV ₁ /FVC, MEF 25/75 ↑ Airway reversibility to albuterol ↑ Blood eosinophil count (in severe refractory asthma)
Bachert, 2012 [39]	166 Severe asthma 152 Non severe asthma 69 Controls	41.3	SEs mix (SE-A, SE-C, TSST-1) ≥ 0.01 kU/L	Asthma OR: 7.26 (95% CI: 2.76–19.13; p < 0.001) Severe asthma OR: 11.09 (95% CI: 4.14–29.68; p < 0.001)	↑ Oral steroid use ↑ Hospitalizations ↓ FEV ₁
Tanaka, 2015 [41]	23 Uncontrolled asthma 59 Poor controlled asthma 90 Controlled asthma	56.1	SE-A, SE-B > 0.35 kU/L		↑ FeNO (with SE-A-IgE) ↓ ACT (with SE-A-IgE)
Matsumoto, 2016 [44]	224 Asthma	62.3	SE-A, SE-B ≥ 0.35 kU/L		↑ Fixed airflow limitation ↑ FEV ₁ annual decreases (in non-atopic asthma) ↑ ACT < 20 ↑ Periostin ↑ ECP ↑ Blood eosinophil count ↑ Sputum eosinophils % ↑ Blood eosinophil count
Song, 2016 [45]	249 Asthma 98 Controls	66.3 68.4	SEs mix (SE-A, SE-C, TSST-1) ≥ 0.01 kU/L	Severe asthma OR: 7.47 (95% CI: 1.86–30.03; p = 0.005)	
Nagasaki, 2017 [46]	23 Current smokers with asthma 40 Ex-smokers with asthma 118 Never smokers with asthma	58 59 52	SE-A, SE-B ≥ 0.01 kU/L	Current smokers with asthma OR: 3.99 (95% CI: 1.52–11.2; p = 0.005)	↑ Airway reversibility (in current/ex-smokers with SE-B-IgE) ↑ Blood eosinophil count (in current/ex-smokers with SE-B-IgE) ↑ GINA treatment step 5 (in current/ex-smokers with SE-A-IgE) ↓ FEV ₁ , FEV ₁ /FVC (in current/ex-smokers with SE-A-IgE)

CRSsNP/CRSwNP, the second group with high IL-5 levels, strongly increased asthma prevalence and almost exclusive CRSwNP. In the latter group, two clusters showed the highest IgE production and asthma prevalence with all samples expressing IgE toward SEs [36].

4. SEs and asthma

Several studies have investigated the relationship of SEs sensitization with asthma and especially with severe asthma (Table 1). European and Asiatic population-based epidemiologic studies and a recent meta-analysis have demonstrated that sensitization to SEs is significantly associated with asthma in the general population [2,3,37]. The GA (2) LEN study showed that the sensitization to SEs is common in European adults, occurs independently from the sensitization to other common aeroallergens, and is associated with high total IgE levels and asthma [2].

In a pediatric population, followed from birth to 5 years, Semic-Jusufagic found an association between SEs sensitization and bronchial hyperresponsiveness [5]. Lee also revealed that sensitization to SE-A and -B is related to the degree of airway hyperresponsiveness, as measured by methacholine PC20 [38].

Bachert found that the sensitization rate to SEs is higher in severe asthmatic patients compared to mild asthmatics and healthy subjects, suggesting that the presence of IgE to SEs, but not against inhalant allergens, represents a risk factor for asthma severity [39]. Kowalsky and Tanaka, using a higher serum IgE SEs sensitization cut off, did not observe a difference in the percentage of SEs sensitized patients between severe and non severe asthmatic patients, but they demonstrated that the mean levels of serum IgE to SEs were higher in severe asthmatics [40,41]. In addition, recent studies have reported an association between SEs-IgE levels and several features of asthma severity, such as need for oral steroid use, hospitalization and impaired lung function

[39,40]. Finally, Tanaka demonstrated that the presence of IgE to SE-A was associated with both poor asthma control and a higher level of fractional exhaled nitric oxide (FeNO) [41].

Recent studies have underlined an association between SEs sensitization and specific phenotypes and endotypes of asthma. Serum IgE to SEs were detected in a significant proportion of patients affected by non-atopic severe asthma [39]. It is well known that about one third of severe asthmatic patients with negative skin prick test to common aeroallergens have increased total serum IgE levels [42]. Barnes suggested a role played by local IgE antibodies synthesized against epitopes expressed by infectious agents such as *S. aureus* in the pathogenesis of non-atopic asthma [43]. Furthermore, Matsumoto stratifying asthmatics according to the atopic status and age of asthma onset demonstrated a significantly higher serum total IgE and periostin levels among non-atopic and/or late-onset asthmatic patients sensitized to SEs [44]. Song found a relation between SEs sensitization and late onset eosinophilic severe asthma with CRS comorbidity in elderly patients [45]. These findings can be probably related to the role played by *S. aureus* in inducing ILC-2 activation and eosinophilic inflammation characteristic of specific endotypes of both CRS and severe asthma.

In current or ex-smoking asthmatics, the frequency of sensitization to SEs, but not to other aeroallergens, is significantly higher than in non-smokers and it has been associated with eosinophilic inflammation and more severe disease [3,46]. The sensitization to SEs decreases in association with smoking abstinence [46]. Two potential mechanisms have been proposed to explain this finding: the increased colonization rate of *S. aureus* in the airways of smokers and the increased release of type 2 cytokines such as TSLP by epithelial cells in response to microorganisms [47–49].

In vitro and *in vivo* studies support the role of SEs-IgE in asthma pathogenesis. Nasal SE-B administration determined allergen sensitization and airway inflammation in ovalbumin-induced murine asthma [50] and promoted non-allergic eosinophilic asthma by itself in dose-response experiments in mice [51]. In another animal model, allergic airway inflammation mediated by IL-17A was induced by epicutaneous SE-B exposure [52]. In conclusion, these animal studies have demonstrated that the local application of small concentrations of *S. aureus* superantigens can induce an inflammatory response in lung suggesting a potential mechanism of both allergic and non-allergic asthma.

5. SEs and COPD

Recent evidence suggests a role of *S. aureus* in the pathogenesis of COPD. Rohde detected significantly higher levels of serum IgE to SEs in both stable and exacerbated COPD patients compared to smokers without COPD and healthy subjects. During hospitalization for COPD exacerbation, IgE to SEs significantly decreased along with the improvement of FEV₁ [53]. The production of IgE to SEs may be related to *S. aureus* colonization observed in the lower airways in COPD [54]. This data indicates a role of *S. aureus* superantigens as a trigger of chronic inflammation in COPD [53].

6. Biological therapy: Recent evidence and future perspectives

Target therapy is the gold standard for the treatment of severe asthma and different biological drugs have been approved: Omalizumab for atopic asthma, Mepolizumab, Reslizumab and Benralizumab for eosinophilic asthma and Dupilumab for eosinophilic and corticosteroid dependent asthma. These drugs have demonstrated to reduce the frequency of asthma exacerbations, the need of oral corticosteroid use and to improve asthma related quality of life and lung function [55–57]. The observation that a similar inflammatory process occurs in both upper and lower airways put the basis for the treatment with biological drugs of recalcitrant CRS to medical and surgical treatment [58–60]. Pinto demonstrated that Omalizumab improved the sino-nasal outcome test in subjects with CRS [61]. Rivero

and Liang, in a systematic review showed that in patients with severe asthma and CRSwNP, Omalizumab and Mepolizumab reduced significantly nasal polyps score [62]. Trials with mepolizumab in patients affected by CRS demonstrated reduction in NP size and need for revision surgery [63,64]. Reslizumab showed to improve nasal polyp score and symptoms in patients with higher nasal secretions levels of IL-5 [65]. Phase III trials of Mepolizumab and Benralizumab in CRSwNP and Reslizumab in CRS are still ongoing [66–68]. Preliminary data of phase III trials of Omalizumab and Dupilumab in CRSwNP patients showed an improvement of either nasal polyp scores and nasal congestion symptoms [69–72]. SEs sensitization can induce a local synthesis of polyclonal IgE that can be reflected by an increase in serum total IgE, and, as we mentioned above, the local IgE antibody synthesis can play a role in the pathogenesis of intrinsic asthma [43]. Several studies have shown the efficacy of omalizumab in severe, difficult-to-control, non-atopic asthma [73,74]. In particular, Pillai demonstrated that omalizumab reduced bronchial mucosal IgE positive mast cells and improved lung function in non-atopic asthmatics [75]. Moreover, the IDENTIFY project recently showed that among 362 severe asthmatic patients previously considered non-atopic on the basis of standard aeroallergen test, 83 patients had IgE against SE-A and/or SE-B and 27 were only sensitized against SEs [76]. Thus, Omalizumab, a monoclonal antibody anti-IgE, could represent a therapeutic approach in patients affected by severe asthma and/or CRS sensitized to SEs [76]. Assessing serum IgE against SEs can be highly recommended in severe asthmatic patients particularly in those defined “non atopic” on the basis of the negativity of the skin prick tests to common aeroallergens, who do not represent, actually, candidates for this treatment. *S. aureus* can induce a type 2 polarization of both adaptive and innate immune systems with IL-5, IL-4, IL-13 playing a key role in inducing eosinophilic inflammation and rhinosinus in patients affected by severe asthma and/or CRSwNP. SEs sensitization was observed particularly in the late onset eosinophilic asthmatic patients with CRS [45]. However, no data on IL-5, IL-4 and IL-13 target therapies in *S. aureus* sensitized patients have been performed. A role of TSLP and IL-33 has been demonstrated in the pathogenesis of severe asthma and Lan showed that these cytokines can be released by epithelial cells damaged by *S. aureus* [24]. Preliminary data suggest that Tezepelumab, a monoclonal antibody anti-TSLP, is able to reduce asthma exacerbations and another trial is still ongoing [77,78]. Phase II studies investigating safety and efficacy of monoclonal antibodies that block IL-33 receptor are completed in both asthma and in CRS but the results are not yet available [79,80]. The potential role of the *S. aureus* in severe asthma pathogenesis and the target therapy that could block these ways are summarize in Fig. 1.

7. Conclusions

S. aureus may play a pathogenetic role in several chronic airway disorders. SEs can induce a polyclonal IgE response and have been recently associated with the eosinophilic endotypes of both nasal polyps and late onset severe asthma. Studies investigating the effect of biological therapies in SEs sensitized patients should be performed in order to better define the association of *S. aureus* with different endotypes of severe asthma and/or CRS.

Conflicts of interest

The Authors have no conflict of interest to declare with this manuscript.

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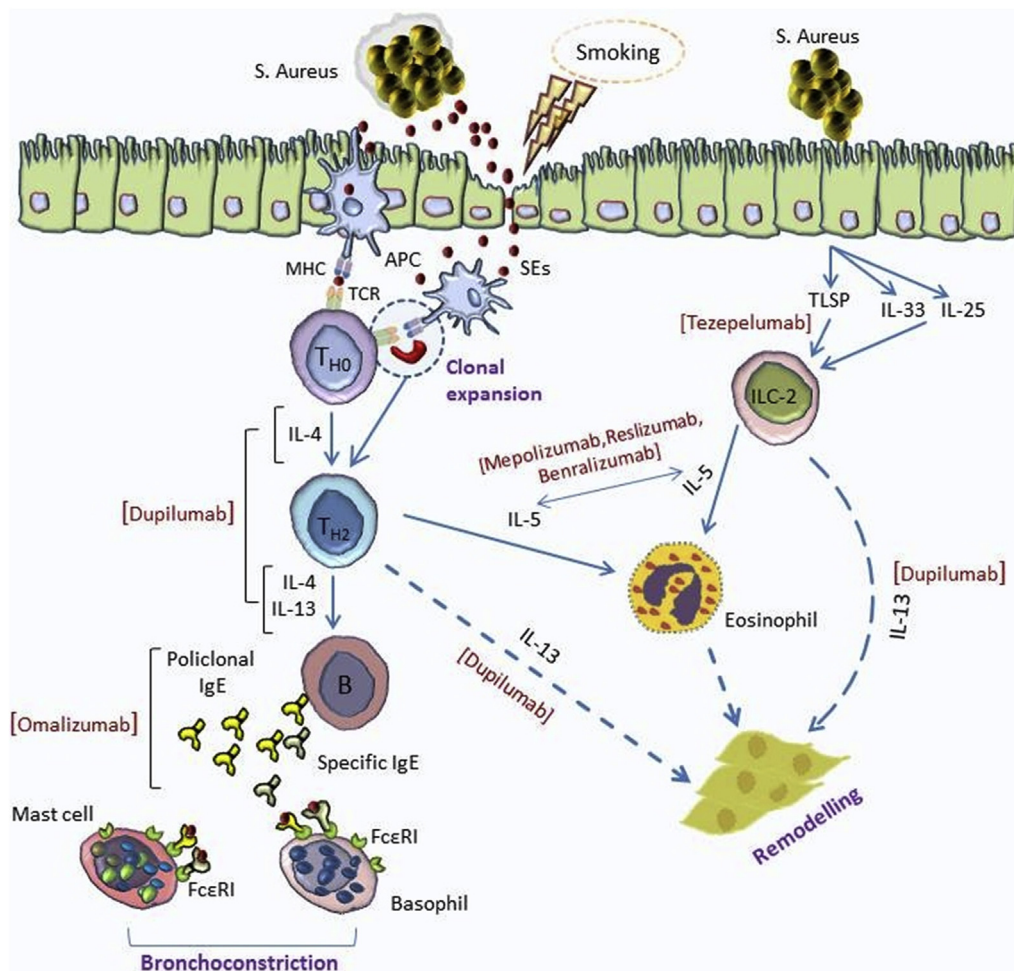


Fig. 1. *S. aureus* and Severe Asthma pathogenesis: potential therapeutic implications.

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