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The relevance of staphylococcal enterotoxins in the progressive course of allergy associated diseases

Introduction

Staphylococcus aureus is frequently found on the epithel of the nose and the skin. Approximately 20% of the population are persistent carriers [1]. Since it occurs as a commensal of the skin flora this colonization is not an indication for an infection, but it bears a risk for a future infection [2]. Especially the increased occurrence of methillin-resistant Staphylococcus aureus (MRSA), which are often multi-resistant to antibiotics, tightens this problem [3, 2].

Staphylococcus aureus can cause illnesses from mild skin infections to life-threatening diseases, thereby plays the secretion of exotoxins a key role in pathogenicity. The pathogen is known to produce factors that trigger inflammation and cause a dysregulation of the immune system, leading to a massive production of cytokines [4, 5]. The Cytokines can, released in high concentration into the blood cycle cause a multiple organ failure or a systemic shock syndrome [6].

The S. aureus enterotoxins A (SEA), B (SEB), C (SEC), D (SED) and TSST-1 (Toxic Shock Syndrom Toxin-1) belong to the group of so-called superantigens. These agents modify the immune response through a massive activation of polyclonal B-cell and T-cell lymphocytes, resulting in a large secretion of IgE [7, 8].

Nevertheless, the enterotoxins can act as classic allergens and SEA-, SEB- SEC-, SED- and TSST-1-specific IgE antibodies can be found in sera and in tissue samples of infected patients [9,10 and 11]. Binding of superantigen-specific IgE to the respective superantigen results in the activation of basophils [9], this might be an essential step in the IgE-mediated inflammation [12].

The role of Staphylococcus aureus in atopic dermatitis

Atopic dermatitis is a chronic relapsing skin disease and characterized by chronic inflammation, itching and lesions, 15% to 20% of the children are affected [13, 14]. The disease is often associated with secondary bacterial infections. One of the most common bacteria, found on the skin of atopic dermatitis patient, is Staphylococcus aureus [15]. Studies revealed that the colonization with Staphylococcus aureus is associated with a higher severity of atopic dermatitis [9, 16]. Specific IgE antibodies to enterotoxin A, B and TSST-1 could be found in many sera of patient with atopic dermatitis [9, 16, 17 and 18]. Patients with high positive rates of SEA/SEB-specific IgEs were found to be school children, severe cases, patients with high serum concentration of total-IgE, cases with exacerbation in summer and patients with cats or dogs as pets [17]. Additionally, levels of specific IgE to food and air allergens were significantly higher [16].
Studies with basophils, isolated from atopic dermatitis patients, suggest that some patient mount an IgE response to Staphylococcus aureus enterotoxins due to the colonization of the pathogen. These toxins may aggravate atopic dermatitis by activating mast cells, basophils, and/or other Fc epsilon receptor bearing cells armed with relevant IgE antitoxins [9].
In some atopic dermatitis patients two other Staphylococcus aureus proteins are expressed, exfoliative toxin A (ETA) and alpha-Toxin [19, 20]. ETA is a major virulenz factor of Staphylococcus aureus and is involved in the emergence of bullous impetico and the staphylococcal scalded skin syndrome [21]. The fact that ETA could be isolated from the sera while ETA-specific IgE antibodies could not, suggests that ETA triggers atopic dermatitis by a not IgE-mediated mechanism [19]. Patients colonized with alpha-toxin producing Staphylococcus aureus had a higher severity of atopic dermatitis and a higher frequency of asthma [20].

The role of Staphylococcus aureus in airway diseases

Newer studies concentrate on the role of the Staphylococcus aureus superantigens in the pathogenesis of airway diseases, like allergic rhinitis, nasal polyposis and asthma. The fact that some atopic dermatitis patients also have bronchial asthma or allergic rhinitis led to the

questions, if there is an association between the sensitisation to staphylococcal enterotoxins and the development of allergic airway diseases [22].

A study revealed a correlation of the presence of serum SEA-, SEB-, SEC-, SED- and TSST-1- specific IgE antibodies and the serum level of the eosinophil cationic protein (ECP) [11]. ECP is part of the immune response against helminth, bacteria and viral infections, but is also attributed with cytotoxic, neurotoxic and fibrosis promoting functions [23]. An elevated ECP level is often associated with allergic asthma and allergic rhinitis and therefore taken as a control parameter for the progress of an asthma therapy [23].

Accessory studies suggest that staphylococcal enterotoxins might play a role in the exacerbation of airway diseases, inflammation of allergic asthma and rhinitis as well as in the development of airway hyper responsiveness in asthma [21, 24, 25 and 8]. The aggravation of pulmonary diseases is presumably mediated with a massive IgE formation in the airways, resulting in a constant degranulation of mast cells present in the affected tissue [8, 26].

Animal models put forward that staphylococcal enterotoxins have the potency to induce or modulate disease [8, 7]. In mices parallel endonasal application of ovalbumin and SEB led to the sensitisation to ovalbumin, the production of ovalbumin-specific IgE antibodies and a following bronchial inflammation with qualities of allergic asthma [7].

While there is an understanding for the importance of staphylococcus aureus enterotoxins in asthma pathogenesis [24] their role in the development of nasal polyposis is discussed controversial [27, 28 and 29].

Staphylokinase: A staphylococcal protein in thrombolytic therapy

Thrombosis is the blockage of blood vessel with clots, consisting mainly of platelets, thrombin and fibrin. Clinical syndromes that can result are acute myocardial infarction and acute ischemic stroke [30, 31]. Thrombolysis could favourable influence the outcome of theses diseases [32]. Thrombolytic agents are agents that transfer plasminogen in the active form plasmin a broad-spectrum plasmolytic protein, which breaks up fibrins and thereby dissolves the clot [30, 32].

The protein staphylokinase is a crucial tool for staphylococcal resistance to host innate immunity. It interacts with bactericidal proteins of the host, thereby abolishes their

bactericidal properties and facilitates bacterial infiltration in the adjacent tissue [30]. The later is promoted by the conversion of host peptide plasminogen to plasmin [33]. This fibrinolytic quality makes staphlokinase interesting for the application in thrombolytic therapy [32]. Because of its high toxicity and antigenic nature great effort was done to achieve recombinat staphylokinase, with better antithrombin and antiplatelet properties and a lower antigenic nature [34, 35 and 36].

Conclusion

The evaluation of staphylococcal enterotoxin-specific IgE antibodies by use of Mediwiss Analytic test membranes can have an additional explanatory value for the severity in atopic dermatitis, allergic rhinitis and allergic asthma. Furthermore, it might be significant for the prognosis of the progressive course of these diseases. Still, a high serum level of enterotoxin-specific IgE could also raise the possibility for an increased level of specific-IgE to the antigenic wildtype staphylokinase. This might be important for the choice of a thrombolytic agent.

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