

Bacterial superantigens and inflammatory skin diseases

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Summary

Bacteria seem to play an important role in the induction and maintenance of inflammatory skin diseases such as psoriasis and atopic dermatitis. Toxins from bacteria including *Streptococcus* and *Staphylococcus aureus*, have been shown to function as a new type of allergen termed 'superantigen'. Superantigens bypass the normal control of T-cell activation and activate all T-cell clones bearing certain types of variable chain on the T-cell receptor: this leads to vigorous T-cell activation and cytokine release. These bacterial superantigens may be involved in induction and aggravation of inflammatory skin diseases. Guttate psoriasis is often preceded by a streptococcal throat infection and T cells specific for streptococcal superantigens have been identified in the skin of patients. The skin of patients with atopic dermatitis is often colonized with superantigen-releasing *Staph. aureus*, and application of a staphylococcal superantigen to human skin induces an eczematoid reaction.

Introduction

It is a clinical experience that infection and colonization of the skin with bacteria may lead to aggravation or induction of inflammatory skin diseases. The best known cases are induction of guttate psoriasis following a streptococcal throat infection and aggravation of atopic dermatitis following colonization with *Staphylococcus aureus* (*Staph. aureus*). Ten years ago it was shown that toxins from bacteria, including *Streptococcus* and *Staph. aureus*, function as a new type of allergen termed 'superantigen'.¹ The role of superantigens and the possible mechanisms for the induction of guttate psoriasis and aggravation of atopic dermatitis are discussed in this review.

Bacterial superantigens

Superantigens are characterized by their capacity to stimulate a large number of T cells. In contrast with

conventional antigens, superantigens bypass intracellular processing and bind directly to the major histocompatibility complex (MHC) class II molecule, on the surface of the antigen-processing cell, outside the antigen-binding groove.¹ The superantigen then cross-links the MHC class II molecule on the antigen presenting cell with T cells according to the composition of the variable region of the T-cell receptor V β chain (V β), leading to polyclonal T-cell activation and cytokine release (Fig. 1). T cells belonging to both the CD4 and CD8 subtype are activated. T-cell activation in the presence of superantigens may lead to the activation of several percent of the total T-cell population and thereby activate more than 10–100 times the number of T cells activated in the presence of conventional antigens.

Psoriasis

Several studies indicate that activated T cells play a pivotal role in the pathogenesis of psoriasis.^{2,3} Guttate psoriasis is often preceded by a streptococcal throat infection. A few years ago Leung *et al.*⁴ demonstrated that streptococcal isolates from the throat of patients with guttate psoriasis produce the superantigen streptococcal pyrogenic exotoxin C (SPEC). SPEC is known to stimulate expansion of V β 2 + T cells, and biopsies from

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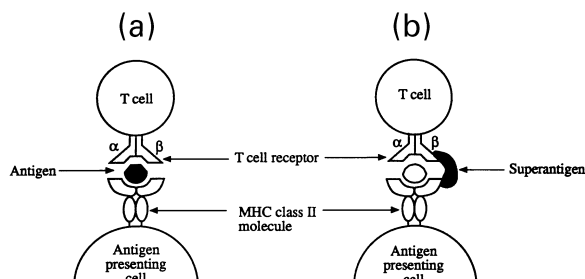


Figure 1 T-cell activation in the presence of peptide antigens (a) or superantigens (b). The peptide antigen binds in the groove of the MHC class II molecule and activates antigen-specific T cells through the T-cell receptor. The superantigen binds to the MHC class II molecule outside the antigen-binding groove and directly cross-links the MHC class II molecule and the V β chain of the T-cell receptor, leading to polyclonal T-cell activation. (Reprinted with permission from *Arch Dermatol* 1995; 131: 830. Copyright 1995, American Medical Association.)

the same patients demonstrated selective upregulation of V β 2 + T cells in the skin. The expansion of V β 2 + T cells occurred in both the CD4+ and CD8+ T-cell subsets. It is therefore hypothesized that superantigens released from the streptococcal throat infection bind to antigen presenting cells in the draining lymph nodes leading to V β 2 + T-cell activation. Bacterial superantigens including SPEC potently induce the expression of the skin homing receptor, the cutaneous lymphocyte-associated antigen (CLA) on T cells.⁵ The V β 2 + T cells expressing CLA may then home to the skin and induce guttate psoriasis in patients with latent psoriasis. Studies have demonstrated increased representation of certain V β expressing T cells in chronic plaque psoriasis compared with blood T cells from the same patient⁶ and an increased number of V β 2 + T cells among CLA+ peripheral blood lymphocytes from psoriasis patients compared with normal subjects.⁷ Furthermore, it has been postulated that the streptococcal superantigen (streptococcal M protein and streptococcal pyrogenic exotoxins) activated T cells cross-react with a skin determinant leading to the expansion of autoreactive T cells.³ In this way superantigen activated T cells may persist in the skin and be involved in chronic plaque psoriasis. The hypothesis is supported by finding of sequence homology between a recombinant streptococcal M protein and the 50 kDa type I keratin.⁸

Atopic dermatitis

Superficial infection and even colonization with *Staph. aureus* may lead to exacerbation of the atopic dermatitis. Leyden *et al.*⁹ found that *Staph. aureus* could be isolated

from 90% of chronic skin lesions in patients with atopic dermatitis, and from all patients with exudative lesions. Increased number of *Staph. aureus* were also found on clinically normal skin of atopic dermatitis patients.⁹ The finding that *Staph. aureus* is increased in number on atopic dermatitis skin and that the degree of colonization correlates to the type of skin lesions has been confirmed by several groups.^{10–12} The role of *Staph. aureus* in atopic dermatitis is supported by the finding that patients with atopic dermatitis who are colonized with *Staph. aureus* have been shown to respond better to a combination of topical steroid and antibiotic therapy than to a topical steroid alone.¹³

Staph. aureus isolated from the skin of patients with atopic dermatitis releases superantigens^{14,15} We have shown that application of the superantigen staphylococcal enterotoxin B (SEB) to intact normal skin and intact atopic skin induce an eczematoid reaction¹⁶ (Fig. 2). In addition, three out of six subjects suffering from atopic dermatitis experienced a flare of their disease in the elbow flexure ipsilaterally to where the superantigen was applied.

Staphylococcal superantigens probably penetrate the injured skin barrier in patients with atopic skin more easily than an intact skin barrier. In the skin superantigens may bind to MHC class II expressing antigen presenting cells, such as Langerhans cells, leading to T-cell activation and cytokine release. Keratinocytes, which in healthy epidermis lack MHC class II molecules, are induced to express MHC class II molecules during inflammation.¹⁷ Such keratinocytes do not have the capacity to process and present conventional antigens to T cells. However, MHC class II positive keratinocytes potently

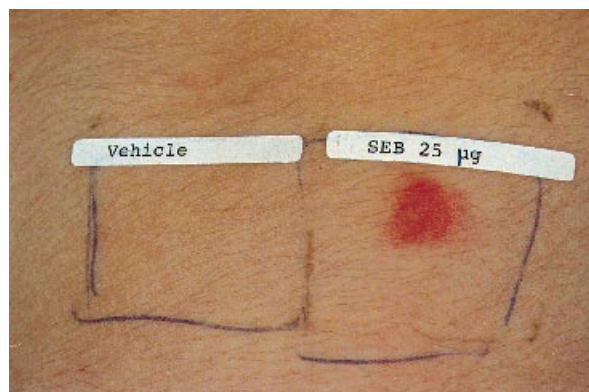


Figure 2 Skin changes following application of the superantigen SEB (25 $\mu\text{g}/\text{cm}^2$) or vehicle (phosphate-buffered saline) under occlusion for 24 h. The photograph was taken 48 h after application of SEB. (Reprinted with permission from *Ugeskrift for Læger* 1999; 161: 4749).

activate T cells in the presence of superantigens^{18,19} This may be of special relevance to patients with atopic dermatitis, as when keratinocytes that are MHC class II positive present superantigens to T cells, preferentially Th2 type cells are activated.²⁰ The Th2 cells are thought to be important for the initiation of atopic dermatitis lesions.^{21,22}

Superantigen-specific T-cell activation is probably responsible for the dermatitis induced by superantigen application, as biopsies from superantigen treated skin demonstrated an up-regulation of T cells expressing V β chains specific for the applied superantigen compared to vehicle treated skin and peripheral blood mononuclear cells (Skov *et al.*, unpublished data). Besides activation of T cells, bacterial superantigens have been shown to induce expression of CLA, which may strengthen homing of T cells to the skin.⁵ In six patients with atopic dermatitis harbouring superantigen producing *Staph. aureus* a relevant superantigen V β skewing within the CLA+ subsets of both their CD4+ and CD8+ T cells in the peripheral blood has been demonstrated.²³ In addition to T-cell activation, superantigens may also activate keratinocytes directly, resulting in the induction of the adhesion molecule ICAM-1²⁴ and release of TNF- α .²⁵

Staph. aureus colonization may also exacerbate atopic dermatitis through another mechanism: up to half of the patients with atopic dermatitis have been shown to produce IgE directed against staphylococcal superantigens.¹⁵ Basophils from normal subjects and patients with atopic dermatitis who lacked IgE anti-toxin failed to release any histamine on exposure to the staphylococcal enterotoxins. In contrast, basophils from patients with atopic dermatitis who produce IgE anti-toxin released histamine on exposure to the relevant enterotoxins but not in response to enterotoxins in which there is no IgE response. In a study of 58 children with atopic dermatitis, 20 patients had IgE against staphylococcal superantigens and the degree of disease severity correlated to a higher extent with the presence of superantigen-specific antibodies than with total serum IgE levels.²⁶ The relevance of IgE antibodies to staphylococcal superantigens may be twofold: (i) IgE specific for superantigens may bind to mast cells or basophils and induce histamine release and thereby induce inflammation; (ii) Langerhans cells in atopic skin, in contrast to normal Langerhans cells, express the high affinity IgE receptor and bind IgE.^{27,28} This binding of antigen-specific IgE to the Langerhans cells has been shown to facilitate and amplify the presentation of aeroallergens to the T cells²⁹ and may be involved in the presentation of superantigens as well.

In addition to stimulating superantigen-specific IgE

production staphylococcal superantigens have been shown to augment allergen-specific IgE production in atopic patients.³⁰

In support of the hypothesis that superantigens may be involved in exacerbation and induction of atopic dermatitis is the finding that other superantigen-associated disorders have been shown to induce dermatitis. Toxic shock syndrome is a disease caused primarily by *Staph. aureus* producing the superantigen toxic shock syndrome toxin 1. Michie and Davis reported that 14 of 68 patients who had survived toxic shock syndrome developed a chronic dermatitis that started 2 weeks after the illness and lasted for over 1 year; in contrast, dermatitis was not a problem after Gram-negative septic shock.³¹ Kawasaki syndrome is a disease that occurs primarily in children and has been associated with superantigens.³² Interestingly, in patients recovering from Kawasaki syndrome an increased prevalence of atopic dermatitis has been reported.^{33,34}

Bacterial infection leads to induction and aggravation of some inflammatory skin diseases. There is strong evidence that superantigens released from the bacteria play a role in the induction and aggravation of the skin diseases, especially guttate psoriasis and atopic dermatitis. Bacterial superantigens have also been related to other skin diseases including cutaneous lupus erythematosus³⁵ and dermatitis herpetiformis.³⁶ The exact mechanism of the interaction between the superantigens and the inflammation is not known; however, superantigen-mediated T-cell activation is most likely because superantigens are extremely potent and may activate up to 20% of all T cells.

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Key points

- Superantigens bypass the normal control of T-cell activation and activate all T-cell clones bearing a certain type of V β chain on the T-cell receptor leading to vigorous T-cell activation and cytokine release.
- The presence of *Staphylococcus aureus* on the skin of patients with atopic dermatitis can exacerbate the skin disease.
- *Staphylococcus aureus* isolated from the skin of patients with atopic dermatitis are shown to release superantigens.
- Application of a staphylococcal superantigen to normal and atopic skin induce dermatitis; T cells specific for the staphylococcal superantigen are upregulated in the skin following application.
- Streptococci from the throat of patients with guttate psoriasis release superantigens; T cells specific for streptococcal superantigens have been identified in the skin of the patients. Thus, superantigens from throat streptococci may trigger guttate psoriasis.